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A CRITICAL SURVEY OF THE NEW YORK PROGRAM FOR THE CARE OF PREMATURE INFANTS

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HISTORICAL INTRODUCTION

THE well-recognized relationship of birth weight to infant mortality rates led to the initiation of a special program for the care of the prematurely born in New York City in 1938. Although spearheaded largely by the Department of Health, the ventures have essentially been cooperative ones with public and private agencies, practicing physicians, nursing and other professional organizations. The initial steps were developed by a small subcommittee of the Advisory Obstetric Council, set up after the New York Academy of Medicine's study of maternal deaths was published in 1933.[1]

Dr. Hugh Chaplin, Dr. Harry Gordon, Dr. Katherine Merritt, and Dr. Hedwig Koenig were among the practicing pediatricians who were particularly active in the early days. The Health Department provided staff and statistical help. Dr. Baumgartner as secretary and Tom Desmond as statistician were also active in committee affairs. Committee members surveyed existing services, set up training institutes and special scientific meetings, developed standards for the care of premature infants, and prepared an infant autopsy manual. Arrangements were made with the visiting nursing services for follow-up care of the baby at home after his discharge from the hospital. Dr. Ethel Dunham of the Children's Bureau and Dr. Edith Potter of Chicago frequently served in advisory capacities.

Since 1939, birth weights have been recorded on the birth certificate with other data relating to the delivery. Individual hospitals were encouraged to keep their statistics according to a uniform scheme and the Health Department regularly provided them with an analysis of their data. The Department of Hospitals and the Health Department jointly made plans for improving facilities for prematurely born infants in municipal hospitals and for training nurses to care for them.

Scholarships were developed so that nurses from both municipal and voluntary hospitals could attend the then available courses for the care of premature infants in Chicago, Baltimore,

From the City of New York's Department of Health.

and Boston. The demand for training opportunities for both doctors and nurses led to the development of a training course in 1949, two weeks for the doctor and one month for the nurse, sponsored by the city and state health departments, the Children's Bureau, and Cornell University Medical College. Slowly the outlines of today's program took shape. Other recommendations, made by the original subcommittee as well as its successor the Pediatric Advisory Committee, to the Commissioner of Health have been implemented in part. These include:

1. *Continuation of Review of Recommended Standards and Practices.*—These standards are maintained by a pediatric advisory committee, composed of leading pediatricians in teaching hospitals and private practice. This committee remains the "watch dog" of the program.

2. *Provision of Consultant Service by the Department of Health.*—It is amusing to recall that in the beginning there was some hesitancy to have anyone except a nurse in a consultant role. Now teams of obstetricians, pediatricians, nurses, and social workers are welcomed.

3. *Establishment of Minimum Standards.*—These standards for the care of premature infants in all hospitals are upheld by regulations adopted by the Board of Health which have the force of law.[2] These cover physical facilities and staff and provide for responsible leadership in each service.

4. *Development of "Approved" Premature Infant Centers.*—The establishment of these centers was greatly aided by Hill Burton funds; the Hospital Council of Greater New York gave such centers a high priority. Centers need not be approved by the Health Department unless they wish to collect public funds for the care of premature infants.

5. *Furnishing Ambulance Service to Transport Premature Infants From Hospital to Hospital or Home.*—

6. *Financial Aid to "Approved" Premature Infant Centers.*—This is designed to aid parents who cannot meet the costs. The money derived (50 per cent from local tax funds and 50 per cent from state reimbursement) is paid at the rate of $16.00 per day for care in an approved center.

7. *Development of a Follow-Up Service After Discharge From the Hospital, Including One Special Foster Home Service.*—

This paper describes in some detail the development of the program, the problems encountered in the past decade, and the attempts to evaluate the results of the program which is probably the largest of its kind: there are more than 165,000 infants born annually, of which 9 per cent (15,000) are born prematurely (2,500 grams or less in weight).

A DECADE OF PROGRESS

World War II retarded the further development of the program and it was not until 1948 that the program originally initiated in 1938 went into high gear. At this time, Standards for the Care of Premature Infants endorsed by the Pediatric Advisory Committee to the Commissioner were revised and distributed to every hospital in the city. Likewise, recommendations for the proper obstetric management as approved and endorsed

by the Obstetric Advisory Committee to the Commissioner were drawn-up and distributed to all physicians and maternity services.[3] The principles were designed for the prevention of infection, maintenance of respiration and body temperature, and proper feeding methods. Hospitals were urged to provide suitable equipment and to train medical and nursing personnel for the immediate care of premature infants. An important new feature was adopted: hospitals which could not meet the standards for adequate and continued care should, with the help of the Health Department, transfer the infants to hospitals which were approved as centers for the care of premature infants.

Such centers were developed because it had been found that not every hospital could maintain a special nursery for premature infants. The need for a staff of highly trained personnel for premature infant care could not be met readily by every hospital owing to the shortage of nurses and to the high financial cost. The physical lay-out and special equipment were other costly considerations. The average hospital would not find it feasible to maintain such a nursery and service for the relatively few infants born prematurely in it. Initially, several hospitals generously shared their facilities with those not as well staffed or equipped and were instrumental in helping to launch the transport service and the further development of other premature centers.[4]

In the past 10 years premature centers have increased in number. At the present time 11 centers are in operation, with the prospect of 2 more when nursing staffs are obtained; additional centers are to be built in the borough of Brooklyn, which has the largest number of premature births, and in the borough of Richmond, which owing to its relative inaccessibility has not been included in the transport service.

The original plan was aimed at establishing 18 to 20 centers with a total capacity of about 500 beds. This estimate was based on the knowledge that about 8 per cent (14 to 15 thousand per year) of all births are premature.

The following formula was used for estimating the required number of beds in premature centers: among the premature infant births, 70 per cent were expected to weigh 2,001 to 2,500 grams. It was believed that most of these infants could be cared for in the hospitals of birth and that most would not need "center" care. Occasionally an infant born prematurely to a diabetic mother might exceed 2,500 grams and still require specialized care in a premature center. It was estimated that the average stay of an infant in a center would be about one month.

At present, 11 premature centers are in operation with a capacity of 327 beds (Table I). However, owing to nursing shortages several centers have not been able to function at full capacity, and the actual number of beds in use approximates 263.

Section 110 of the Sanitary Code pertaining to maternity and newborn infant services has, since 1953, incorporated regulations regarding care of premature infants.[2] These relate to the physical lay-out, equipment, and staffing. It is not mandatory to transport infants to premature centers, but

any hospital choosing to care for its own premature infants must provide adequate care in accordance with the regulations of the Sanitary Code. The program is, thus, voluntary in nature, and a premature birth is not regarded reportable per se, as it is in some communities. However, the Department of Health possesses full knowledge of all premature births in New York City since every birth certificate filed with the Department includes the infant's birth weight.

Table I. Growth of Premature Centers From 1948 to 1957

HOSPITAL	TYPE	OPENED	LOCATION	APPROVED FOR PAYMENT	THEORETIC CAPACITY	PRESENT OPERATING CAPACITY
New York	Voluntary	Before 1948	Manhattan	July 1, 1950	22	22
Flushing	Voluntary	1948	Queens	July 1, 1950	30	14*
Babies	Voluntary	1949	Manhattan	July 1, 1950	23	23
St. Vincent's	Voluntary	1949	Manhattan	July 1, 1950	30	30
Lincoln	Municipal	1949	Bronx	July 1, 1950	16	16
Harlem	Municipal	1950	Manhattan	November 1, 1950	40	40
Queens General	Municipal	1950	Queens	November 15, 1954	21	15*
Bellevue	Municipal	1951	Manhattan	November 26, 1952	30	24*
Kings County	Municipal	1952	Brooklyn	November 26, 1952	40	35*
Mt. Sinai	Voluntary	1953	Manhattan	January 1, 1954	41	22*
Long Island Jewish	Voluntary	1956	Queens	July 1, 1956	34	22
					327	263

*The operating capacity of these centers has not reached full expansion as yet because of shortage of nurses.

Concurrent with the Premature Transport Program, there has been a continuous educational program through the hospital consultation service regarding the proper management of premature labor and delivery as well as of premature infant care. Each of the 98 hospitals in the City with maternity and newborn infant services are visited periodically by a consultant team of the Maternity and Newborn Division of the Department of Health. The team includes obstetric, pediatric, nursing, and social work consultants. In reviewing services and making recommendations, it is a function of the consultants to further indoctrinate, train, and to provide experience for the nursing staff in the care of premature infants. Such training facilities are available in several premature centers. By such means, the standards for care of the premature infant have been promoted on a city-wide basis. As a result, it is unusual to encounter flagrant errors in premature care today, a situation which did not prevail 10 years ago. However, the fact remains that the average hospital cannot render adequate care for the premature infant and, thus, needs the help of the premature centers.

PREMATURE TRANSPORT SERVICE

In order to expedite the transfer of the premature infants to approved centers, the New York City Department of Health in cooperation with the Department of Hospitals inaugurated a Premature Transport Service in November, 1948.[5] The Department of Hospitals provides a specially designed

and equipped ambulance with trained ambulance drivers. The Department of Health is responsible for staffing the transport service with public health nurses, specially trained in the care of the premature infant. The Department of Health also provides the services of a clerk responsible for accepting calls, dispatching trips, and checking with each center regarding available vacancies. The transport of the infant is safeguarded in every possible way, and the fundamental requirements of maintenance of body warmth and respiration are carefully adhered to. Oxygen is given as needed in controlled concentration and carefully checked to be certain that it does not exceed 40 per cent. The nurse's sole responsibility in the course of transporting the infant is to watch the infant and administer to his needs. Not infrequently, respiratory difficulty is relieved when the watchful experienced nurse notes an accumulation of secretion and promptly aspirates, clearing the airway. The nurse's bag contains necessary equipment for aspiration as well as emergency drugs such as adrenalin and caffeine which are seldom needed. The service operates on a 24-hour basis, 365 days a year. It is of interest that the majority of requests for placement comes from private physicians. Every category of hospital in the City (municipal, federal, voluntary, and proprietary) utilizes the transport service. A tendency has been noted in the last 4 years for a decline in the number of calls to the home which parallels the decline in home deliveries.

In the 10 years since the inauguration of the program, 8,511 infants have been transported to centers from home or hospital, including 712 sets of twins and 25 sets of triplets. The premature centers cared for these infants in addition to those born in their own hospitals. The transported infants are cared for in the same general unit as the infants who are born within the hospital.

SELECTION OF INFANTS FOR TRANSPORT TO PREMATURE CENTERS

Infants born at home have priority for the transport service. Generally, the home conditions in these cases are unsuitable, and, therefore, it is important to move the infants as promptly as possible. Very small infants are next in order of priority, and infants in a debilitated and critical condition regardless of weight have next consideration. Reliance must be placed on the judgment of the doctor requesting the transport. If it is felt that the infant is not moribund and can be transported, his request is honored. Whenever possible, the infant is transported to the center nearest his home or hospital of birth. This is not always feasible since vacancies in the centers

TABLE II. TRANSPORT SERVICE FOR PREMATURE INFANTS FROM NOVEMBER 1, 1948, TO OCTOBER 31, 1958, INCLUSIVE

YEAR	TRANSPORT REQUESTS	BABIES PLACED	PER CENT OF REQUESTS GRANTED
1948 (2 months)	96	94	98
1949	642	560	87
1950	887	691	78
1951	1,095	825	75
1952	1,114	784	70
1953	1,116	897	80
1954	1,143	978	86
1955	1,095	891	81
1956	1,146	929	81
1957	1,276	1,053	82
1958	1,028	809	79
Totals	10,638	8,511	80

frequently determine the placement of infants. The number of requests for placement and babies transported each year is depicted in Table II; the number of hospitals utilizing the service is listed in Table III; the number of infants transferred to and from the respective boroughs of the City is listed in Table IV. Since most of the centers (6 out of 11) are located in Manhattan, most infants are transported to this borough, even though the borough of birth may be other than Manhattan.

TABLE III

A. Hospitals Utilizing the Transport Service for Premature Infants

	UTILIZE SERVICE	DO NOT UTILIZE SERVICE	REQUESTS FOR 1957	PER CENT OF TOTAL
Proprietary	24	0	344	27
Voluntary	44	15 (7 have centers)	456	35
Municipal	10	5 (have centers)	442	35
Home	—	—	25	1
Other	—	—	9	1
Totals	78	20	1,276	100

B. Total Requests From January 1, to October 29, 1958

SOURCE OF REQUEST	SERVICE PATIENTS	PRIVATE PATIENTS
Municipal	383	—
Proprietary	—	269
Voluntary	128	226
Home	7	1
Other	3	—
Totals	521	496

TABLE IV. TRANSPORTS FROM BOROUGH TO BOROUGH IN 1957

FROM:	MANHATTAN	BRONX	BROOKLYN	QUEENS	TOTALS
To:					
Manhattan	281	126	213	50	670
Bronx	20	17	12	1	50
Brooklyn	3	—	43	1	47
Queens	45	34	99	105	283
Totals	349	177	367	157	1,050

PAYMENT FOR SERVICES

No fee is charged for the transport service; the cost of a trip is approximately $26.00. The average length of time an infant is in transit is about one-half hour, although the trip itself may last 3 hours from the time the ambulance leaves the station until it returns.

The care of a premature infant is costly and poses a financial strain on the hospital and the family. It is estimated that current costs of care for a premature infant approximate $25.00 per day. To help defray expenditures on the part of hospital and family, a program of reimbursement when the family is unable to pay for premature infant care in approved premature centers was begun July 1, 1950.[6] Initially, the rate was $12.00 per day. Since 1956, it has been increased to $16.00 per day. In order for the hospital to receive reimbursement, it must comply with the standards and criteria

established by the Pediatric Advisory Committee relative to physical structure, equipment, policies, procedures, and staffing. Approval for payment to a center is then granted on a one-year period and renewed annually following a survey of the center. A liberal and flexible plan of financial eligibility has been devised and is revised periodically in relation to living costs. Families of premature infants in New York City are seldom able to pay for the total cost of care, and payments by them constitute only a small percentage of the total cost. In 1957, 83 per cent of families of premature infants cared for in "approved" premature centers required full financial assistance and an additional 4.7 per cent were given partial assistance. Thus, financial need and the requirement for highly specialized care constitute impelling reasons for a community program for the premature infant.

SURVIVAL OF PREMATURE INFANTS

To determine if the program has saved lives as well as to evaluate progress, data compiled by premature infant centers and data based on New York City birth and infant death certificates have been collected and analyzed. Birth weights are grouped as shown in Table V: 67.7 per cent of all infants born weighing less than 2,500 grams are in the 2,001 to 2,500 gram group; the remaining 32 per cent are distributed among the other 3 weight groups, with 7.5 per cent in the 1,000 gram and under group, 7.4 per cent in the 1,001 to 1,500 gram group, and 17.4 per cent in the 1,501 to 2,000 gram group. This distribution has

TABLE V

A. Births and Deaths Among Premature Infants Born in New York City in 1957

WEIGHT GROUPS (GRAMS)	TOTAL NUMBER	PER CENT OF DISTRIBUTION	NUMBER OF DEATHS	PER CENT OF MORTALITY
1,000 and under	1,142	7.5	1,077	94.3
1,001 to 1,500	1,129	7.4	551	48.8
1,501 to 2,000	2,654	17.4	442	16.7
2,001 to 2,500	10,312	67.7	455	4.4
Totals	15,237	100.0	2,525	16.6

B. Number and Percentages of Live Births Under 2,500 Grams by Weight Groups in New York City in 1957 by Ethnic Groups

	WHITE	PER CENT OF DISTRIBUTION		NONWHITE	PER CENT OF DISTRIBUTION	
1,000 and under	660	6	30	482	10	38
1,001 to 1,500	695	7		434	9	
1,501 to 2,000	1,791	17		863	19	
2,001 to 2,500	7,408	70		2,904	62	
Totals	10,554	100		4,683	100	

C. Infant Deaths Among Infants Born Under 2,500 Grams by Weight Groups in New York City in 1957 by Ethnic Groups

	WHITE	PER CENT	NONWHITE	PER CENT
1,000 and under	631	95.6	446	92.5
1,001 to 1,500	377	54.2	174	40.1
1,501 to 2,000	320	17.9	122	14.1
2,001 to 2,500	340	4.6	115	4.0
Totals	1,668	15.8	857	18.3

been fairly constant through the years, with perhaps a slight proportionate increase recently in the lower weight categories. The percentage distribution in the 4 weight categories reveals a greater proportion of infants in the group under 2,000 grams among nonwhite as compared with the white group. This difference has been constant since 1950. The lower mortality rates for the nonwhite infants in each weight group leads one to speculate regarding the relative maturity of the infants in each group when weight is used as the sole criterion.[7, 8] Studies are currently in process which may define maturity in relation to weeks of gestation as well as to weight. The mortality rates of infants born in hospitals with premature infant centers are lower in each

TABLE VI. BIRTHS AND DEATHS AMONG WHITE AND NONWHITE PREMATURE INFANTS BORN IN HOSPITALS WITH PREMATURE CENTERS IN 1957

WEIGHT GROUPS (GRAMS)	TOTAL NUMBER	PER CENT DISTRIBUTION BY WEIGHT		NUMBER OF DEATHS	PER CENT OF MORTALITY	PER CENT OF CITY-WIDE MORTALITY
A. White and Nonwhite						
1,000 and under	408	12	43	377	92.4	94.3
1,001 to 1,500	322	10		144	44.7	48.8
1,501 to 2,000	733	21		95	13.0	16.7
2,001 to 2,500	1,976	57		54	2.7	4.4
Totals	3,439	100		670	19.5	16.6
B. White						
1,000 and under	133	7	33	127	95.5	95.6
1,001 to 1,500	124	7		68	54.8	54.2
1,501 to 2,000	340	19		51	15.0	17.9
2,001 to 2,500	1,197	67		39	3.3	4.6
Totals	1,794	100		285	15.9	15.8
C. Nonwhite						
1,000 and under	275	17		250	90.9	92.5
1,001 to 1,500	198	12		76	38.4	40.1
1,501 to 2,000	383	24		44	11.2	14.1
2,001 to 2,500	779	47		15	1.9	4.0
Totals	1,635	100		385	23.4	18.3

TABLE VII. COMPARATIVE MORTALITY RATES AMONG

WEIGHT (GRAMS)	CITY WIDE				BORN IN CENTERS			
	TOTAL NUMBER	PER CENT OF DISTRIBUTION BY WEIGHT	NUMBER OF DEATHS	PER CENT OF MORTALITY	TOTAL NUMBER	PER CENT OF DISTRIBUTION BY WEIGHT	NUMBER OF DEATHS	PER CENT OF MORTALITY
1,000 and under	1,142	7.5	1,077	94.3	408	12.0	377	92.4
1,001 to 1,500	1,129	7.4	551	48.8	322	9.0	144	44.7
1,501 to 2,000	2,654	17.4	442	16.7	733	21.0	95	13.0
2,001 to 2,500	10,312	67.7	455	4.4	1,976	57.0	54	2.7
Totals	15,237	100.0	2,525	16.6	3,439	99.0	670	19.5

weight category than they are for the city as a whole; the differences exist for the nonwhite infants as well as for the white ones in each weight group. This differentiation is not apparent in the over-all mortality rates for infants under 2,500 grams. Thus, use of this rate alone for comparative purposes could be misleading since it does not take into consideration the differences in weight distribution of the infants (Table VI, *B* and *C*).

The mortality rates of premature infants transferred to approved centers are compared with those of infants born in the hospitals with centers (Table VII). In 1957, as in previous years, the mortality rates of the transported infants are lower for each weight category under 2,000 grams in comparison to that of the infants born in hospitals with centers. This situation is reversed for the group weighing 2,001 to 2,500 grams, in which the mortality rate for the transported group is generally higher than those of the other 3 categories. The reason for this disparity may be due in part to the fact that infants weighing less than 2,000 grams who survived less than a few hours were seldom transported. On the other hand, in a hospital with a center such infants would be included in the statistics. In the weight group of from 2,001 to 2,500 grams the explanation for the higher mortality rate for the transported infants may be that infants in this group are seldom transferred to centers unless an additional health problem exists.

The mortality experience with infants in the several weight categories for whom transport to premature centers was not requested is shown in Table VII. The mortality rates for this group in every weight category are higher than for infants born in hospitals with centers. The mortality rates of the "nonrequested" group are also higher than in the group of infants who were transported to premature infant centers. The increase is noted in every weight category except in the 2,001 to 2,500 gram group.

In each weight group the mortality rate of infants born in Richmond is higher than that of infants in comparable weight groups born in hospitals with centers (Table VI, *A* and *B*).

Data for previous years comparing this borough's mortality rates of premature infants and those of hospitals with premature centers are similar and

PREMATURE INFANTS BORN IN 1957 IN NEW YORK CITY

TRANSPORTED TO CENTERS*				TRANSPORT REQUESTED BUT NOT PROVIDED				TRANSPORT NOT REQUESTED			
TOTAL NUMBER	PER CENT OF DISTRIBUTION BY WEIGHT	NUMBER OF DEATHS	PER CENT OF MORTALITY	TOTAL NUMBER	PER CENT OF DISTRIBUTION BY WEIGHT	NUMBER OF DEATHS	PER CENT OF MORTALITY	TOTAL NUMBER	PER CENT OF DISTRIBUTION BY WEIGHT	NUMBER OF DEATHS	PER CENT OF MORTALITY
108	9	76	70.4	33	14.7	32	97	593	5.7	592	99.8
361	32	92	25.5	38	17.4	35	92	408	3.9	280	68.6
535	49	46	8.6	104	46.4	33	32	1,282	12.2	268	20.9
107	9	8	7.5	48	21.5	2	4	8,181	78.2	391	4.8
1,111	99	222	20.0	223	100.0	102	46	10,464	100.0	1,531	14.6

*This category includes all infants moved by the city Premature Transport Ambulance and by private ambulances.

give further credence to the hypothesis that the premature infant program has resulted in an increased survival of infants.

It will be of interest to watch progress in this borough when care in developed substantiate the favorable effects of center care in increasing survival rates.[9]

It appears that on a city-wide basis the emphasis given to principles of proper management of premature la-

TABLE VIII. MORTALITY RATES OF INFANTS UNDER 2,500 GRAMS BORN AND CARED FOR IN THE BOROUGH OF RICHMOND COMPARED WITH THOSE OF INFANTS BORN IN HOSPITALS WITH PREMATURE CENTERS

WEIGHT GROUPS (GRAMS)	RICHMOND				BORN IN HOSPITALS WITH CENTERS			
	BIRTHS	PER CENT OF DISTRIBUTION BY WEIGHT	DEATHS	PER CENT	BIRTHS	PER CENT OF DISTRIBUTION BY WEIGHT	DEATHS	PER CENT
1,000 and under	14	5	14	100.0	408	12+	377	92.4
1,001 to 1,500	22	8	13	59.0	322	9+	144	44.7
1,501 to 2,000	62	21	12	19.3	733	21+	95	13.0
2,001 to 2,500	194	66	10	5.1	1,976	57	54	2.7
Totals	292	100	49	16.8	3,439	99+	670	19.5

TABLE IX. MORTALITY RATES BY WEIGHT GROUPS FOR INFANTS BORN IN NEW YORK CITY, WEIGHING 2,500 GRAMS OR LESS, FROM 1947 TO 1957

	1,000 GRAMS		1,001 TO 1,500 GRAMS		1,501 TO 2,000 GRAMS		2,001 TO 2,500 GRAMS	
	NUMBER BORN	PER CENT DIED	NUMBER BORN	PER CENT DIED	NUMBER BORN	PER CENT DIED	NUMBER BORN	PER CENT DIED
1947	778	95.0	1,048	60.7	2,492	21.1	10,339	5.4
1948	736	96.8	1,007	60.0	2,513	23.3	9,670	5.3
1949	828	96.9	952	48.6	2,458	19.3	9,572	5.2
1950	938	96.8	977	46.3	2,459	17.7	9,413	4.9
1951	967	93.9	1,021	53.0	2,495	16.6	10,074	4.4
1952	1,020	92.6	1,107	47.3	2,516	15.6	10,091	4.6
1953	1,006	92.3	1,132	48.5	2,527	16.7	9,826	4.6
1954	1,056	92.5	1,055	51.6	2,540	16.7	9,723	4.3
1955	1,047	95.7	1,216	52.2	2,592	17.2	10,298	4.7
1956	1,098	95.7	1,065	52.1	2,495	16.5	9,996	4.8
1957	1,142	94.3	1,129	48.8	2,654	16.7	10,312	4.4

TABLE X. PER CENT OF MORTALITY IN INFANTS WEIGHING 2,500 GRAMS OR LESS FROM 1947 AND 1948 TO 1957*

	1,000 GRAMS OR LESS		1,001 TO 1,500 GRAMS		1,501 TO 2,000 GRAMS		2,001 TO 2,500 GRAMS	
	BIRTHS	PER CENT OF MORTALITY	BIRTHS	PER CENT OF MORTALITY	BIRTHS	PER CENT OF MORTALITY	BIRTHS	PER CENT OF MORTALITY
1947	778	95.0	1,048	60.7	2,492	21.1	10,339	5.4
1948	736	96.8	1,007	60.0	2,513	23.3	9,670	5.3
1957	1,122	96.0	1,129	48.8	2,654	16.7	10,332	4.4

*Also see Fig. 1.

premature infant centers becomes available. Comparison of premature infant mortality rates from various hospitals before and after centers were

bor and delivery and of the care of the prematurely born infant has been amply justified as evidenced by the mortality rates by weight groups for New

York City in 1947 and 1957. The greatest reduction, however, occurred from 1947 to 1949 (Table IX).

each weight group except in that of the 1,000 gram and under group; this may be attributed to several factors. With

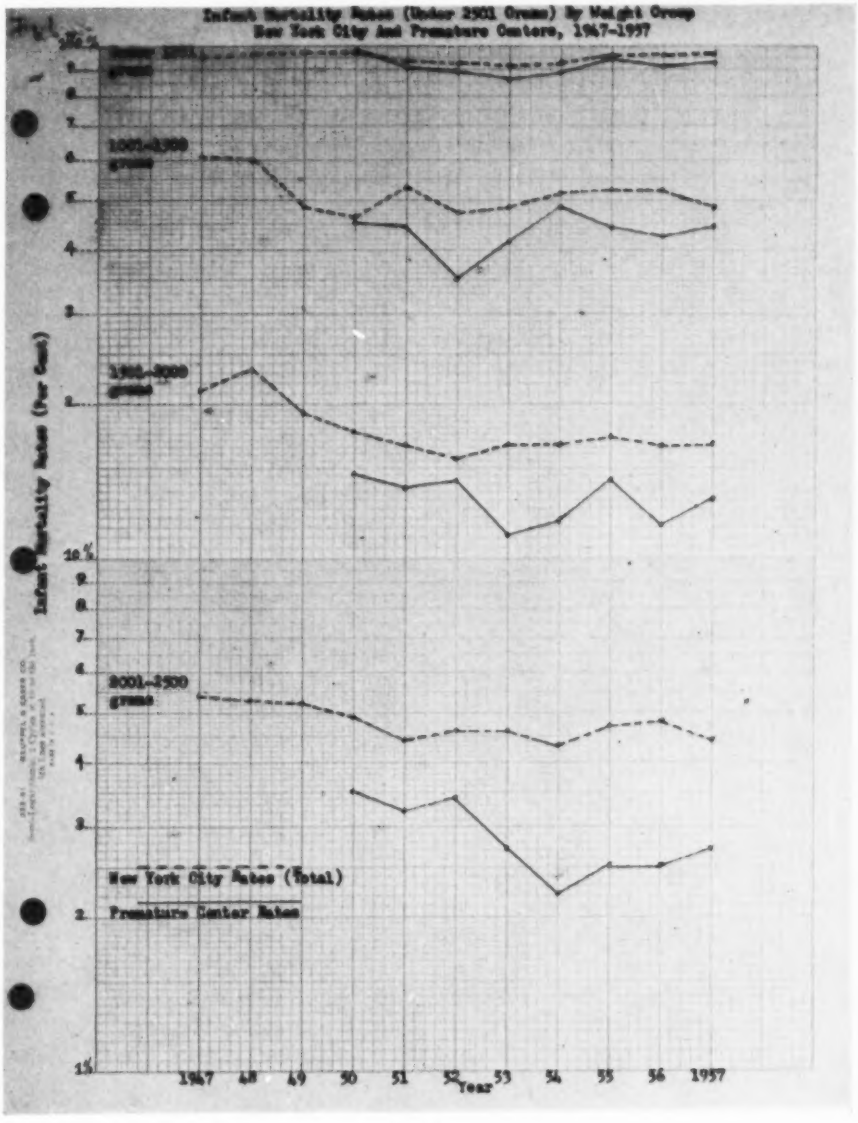

Fig. 1.

In New York City premature infant mortality rates declined perceptibly in

improved obstetrical care and more accurate reporting, more infants are

now probably reported as live births in the "poor risk" category than formerly when proportionately more of them were classified as fetal deaths or stillbirths. This hypothesis finds substantiation in the decline of fetal deaths in the 28 weeks' gestation and over group (Fig. 2). Declines have also occurred in each of the remaining three weight groups since 1947: a 20 per cent decline in the 1,001 to 1,500 gram group; a 21 per cent decline in the 1,501 to 2,000 gram group; a 19 per cent decline in the 2,001 to 2,500 gram group. Individual centers have also noted increasing survival rates as techniques and skills have improved.[10]

The decline in the mortality rate in the 2,001 to 2,500 gram group (19 per cent) is by far the most significant since this group comprises two thirds of all premature infants. In 1947 the mortality rate in this group on a city-wide basis was 5.4 per cent, whereas in 1957 the rate was reduced to 4.4 per cent, a statistically significant decline. If the 1947 mortality rate had prevailed in 1957 for this weight group alone, over 100 premature infants born in 1957 who are alive today would have been lost. It has also been estimated that if the survival rates of premature centers prevailed city wide for all infants weighing 2,500 grams or less, an additional 350 to 400 infants' lives would have been spared in New York City in that year.

It is not possible at this time to include precise comparable mortality rates for the country as a whole or for

TABLE XI. NEONATAL DEATH RATES* BY BIRTH WEIGHT IN SELECTED REPORTING AREAS, 1952 TO 1954

AREA AND COLOR	BIRTH WEIGHT (TOTALS IN GRAMS)				
	UNDER 2,500	1,000 OR LESS	1,001 TO 1,500	1,501 TO 2,000	2,001 TO 2,500
Illinois					
Total	175.0	931.8	520.5	178.5	40.7
White	180.6	939.0	543.5	184.6	42.7
Nonwhite	153.3	900.4	437.3	154.2	33.1
Maryland (exclusive of Baltimore)					
Total	158.3	746.9	539.3	167.7	42.1
White	158.7	768.7	536.5	167.7	42.9
Nonwhite	156.9	680.0	547.8	167.5	39.1
New York State (exclusive of New York City)					
Total	171.2	939.1	548.4	178.6	40.2
White		Not available			
Nonwhite		Not available			
Baltimore (City)					
Total	153.6	870.8	439.5	167.6	33.3
White	157.8	898.0	475.3	207.8	35.1
Nonwhite	148.9	845.0	408.0	123.9	31.1
New York (City)					
Total	144.0	894.4	459.6	141.7	31.7
White	138.4	904.3	483.3	148.3	33.9
Nonwhite	161.9	875.4	401.7	122.0	24.2

The source of data is Vital Statistics, Special Report, Selected Studies, vol. 47, No. 1, U. S. Department of Health, Education, and Welfare.

*Rates are deaths under 28 days per 1,000 live births for specified weight group.

other metropolitan areas. The latest available statistics from reporting areas cover the period of from 1952 to 1954, as shown in Table XI.

It is noted that New York City's neonatal mortality rates are lowest in all reported areas in the 1,501 to 2,000 and the 2,001 to 2,500 gram groups for

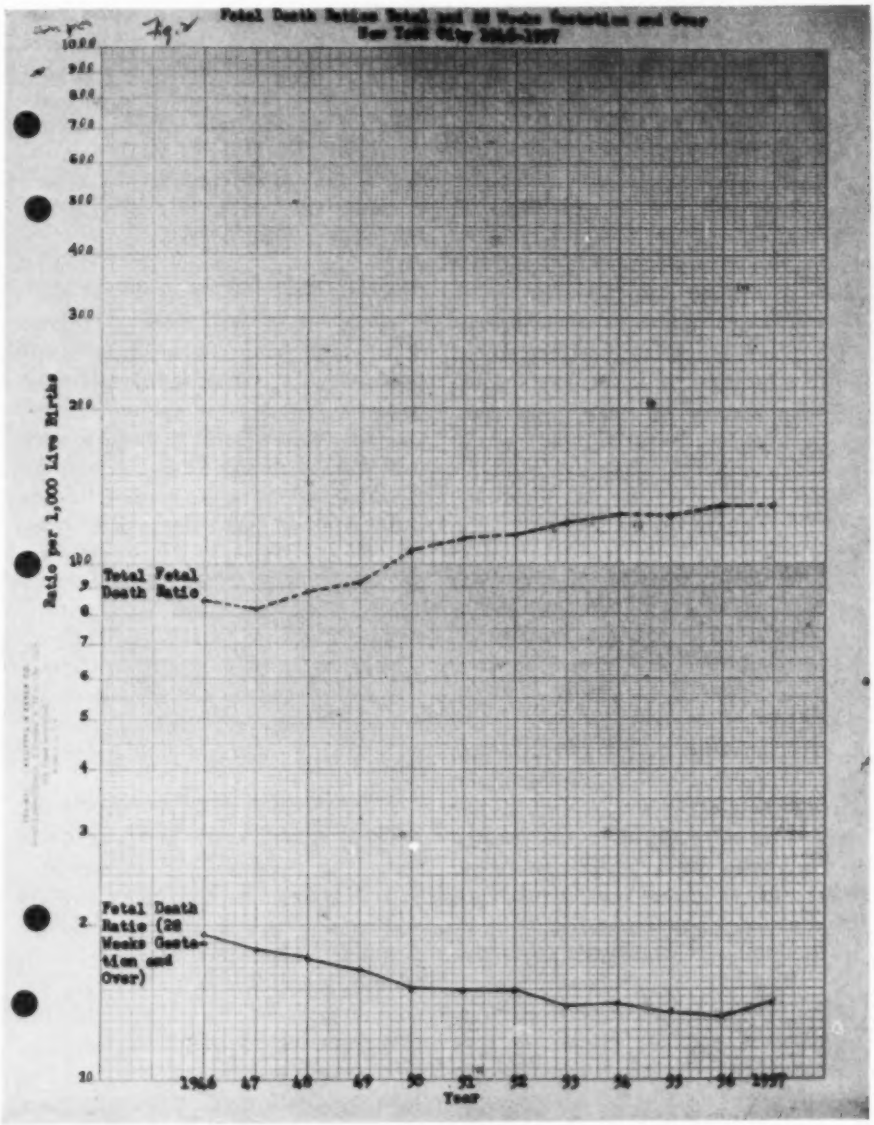

Fig. 2.

all infants and for the white and nonwhite groups. In addition, the New York City nonwhite rate is also lowest in the 1,001 to 1,500 gram group.

It is well recognized that factors other than premature centers have contributed significantly to the improvement of survival rates of premature infants, such as the availability of antimicrobial agents, better nursing care, increased use of transfusions, improved knowledge of nutrition and better methods of feeding, improved incubators, and better aseptic techniques. However, the fact remains that survival rates in approved premature centers are generally higher than in hospitals not maintaining centers.

CARE OF INFANTS FOLLOWING DISCHARGE FROM HOSPITAL

With the knowledge that the prematurely born infant is more vulnerable to environmental factors even after the neonatal period than is his full-term counterpart, the need for intensive follow-up care after discharge from the hospital cannot be overemphasized.[11]

The premature infant is frequently handicapped not only by his premature birth but by being born under circumstances fraught with serious social and economic problems. For these reasons, early and ample social service casework must be available for these infants and their families. Approved premature centers provide such service.

Home visits are arranged through an interagency referral system so that visiting public health nurses have an opportunity to evaluate the home situation prior to the infant's discharge.

In those cases where insurmountable problems exist in relation to parents or to home features or to both, facilities are available through the Speedwell Society for interim foster home care.

Prematurity in itself and the relatively long stay in the hospital beget fears in the parent and a lack of confidence which must be allayed. Therefore, in the hospitals with premature centers the mothers are urged to come to the hospital for instruction so that she may familiarize herself with her baby and his proper care.

FURTHER EMPHASIS ON CARE OF THE "LARGE PREMATURE INFANT"

Although particular attention needs to be aimed at reducing the mortality rates in the 1,500 gram and under category, it is believed that much more emphasis than p r e s e n t l y prevails should be given to the care of infants in the 1,501 to 2,500 gram weight categories. It is reasonable to believe that a significantly greater number of babies could be saved if "center" standards of care could be given to all. This group not only comprises the majority of premature births but includes the ones which have the best potential for normal growth and development.

PREVENTION OF PREMATURITY

There is still much more *unknown* about the prevention of prematurity than is known. In fact, the incidence of premature births has risen slightly in recent years from 7.6 per cent in 1948 to 9 per cent in 1957. This rise may be attributed to the fact that the proportion of births in the nonwhite and in the Puerto Rican populations in relation to the total births has been steadily rising. In 1950, 20 per cent of all births in New York City were to nonwhite and Puerto Rican mothers;

by contrast, in 1957 over 30 per cent of all births were to nonwhite and Puerto Rican mothers. Since the incidence of premature births is relatively high in these two groups (14 to 15 per cent among nonwhites and 10 to 11 per cent among Puerto Ricans), it is not surprising that the city-wide incidence has not declined.[12] An additional factor in maintaining the percentage of premature births is the decline in late fetal deaths (28 weeks' gestation and over) (Fig. 2).

In an analysis of 1,000 records of mothers whose infants were transported in 1957 and 1958, 23 per cent had previous histories of premature births and 35.3 per cent had had some complication of pregnancy. Of the latter, the most common were premature rupture of membranes (12.8 per cent) and vaginal bleeding (11.1 per cent). Abruptio placenta was recorded in 3.6 per cent and placenta previa in 3.3 per cent. Pre-eclampsia occurred in 4 per cent. A history of a medical complication was found in 9.2 per cent. Multiple births were associated with 16.4 per cent. Over 42.4 per cent had late or no prenatal care, and of these, 8 per cent had no care, whereas the city-wide average for births with late or no prenatal care during the same period was 18.5 per cent. The incidence of prematurity in the group which had early and continuous prenatal care is not known at this time; a study is now in progress.

The large proportion of premature births associated with late or no prenatal care serves to highlight the need for providing adequate prenatal care and for education of women to avail themselves of such facilities.[13, 14]

CONTROL OF RETROLENTAL FIBROPLASIA

As soon as it was demonstrated that high concentration and duration of oxygen administration were the major factors in the etiology of retrolental fibroplasia, the Department, early in 1954, took the necessary steps to insure that oxygen was administered only when indicated and in controlled concentrations under 40 per cent. Hospitals were repeatedly advised and cautioned in this regard, with the result that a prompt decline in the number of cases of retrolental fibroplasia occurred.

In 1953, the year *before* the Health Department alerted hospitals and physicians about the problem, 64 infants born in 1953 were classified as blind due to retrolental fibroplasia by the State Commission for the Blind. In 1954 and 1956 the number was reduced to 2 cases per year and in 1957 and 1958 there was only 1 case per year. Thus, this iatrogenic disease, previously the number one cause of blindness in children, is being eliminated.

CONCLUSION

The program for the care of premature infants in approved centers has not only brought about an improvement in the skilled care given to the prematurely born but has had a remarkably stimulating effect on research activity on various aspects of prematurity.

SUMMARY

1. The premature program of the past decade for New York City is described.

2. Statistics relating to mortality rates for premature infants in 4 weight

groupings under 2,500 grams are presented for hospitals with approved premature centers and for the City as a whole.

3. A downward trend is noted in the mortality rate in each weight group, except in the less than 1,000 gram group.

4. Comparison of mortality rates of premature infants (classified by weight groups) born in a borough as yet not included in the premature program with those of infants born in hospitals with centers supports the hypothesis that premature center care increases the survival rate.

5. In each weight group infants cared for in approved centers had a higher survival rate than was the case for the City as a whole.

6. A higher proportion of mothers who delivered prematurely had late or no prenatal care than did those who delivered at term.

7. Emphasis is put on the importance of paying greater attention to the care of the "large premature infant."

8. The need for intensive and continued follow-up care after discharge from the hospital is emphasized.

9. The need for continued and intensified research is indicated.

Grateful acknowledgement is expressed to Miss Freida Greenstein, Senior Statistician, for her help in compiling the statistical data.

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THE STATUS OF 2-YEAR-OLD CHILDREN WHO HAD RECEIVED SULFISOXAZOLE IN THE NEONATAL PERIOD AFTER PREMATURE BIRTH

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IN A previous paper[1] we reported the results of a clinical trial which was designed to test the relative effectiveness of two prophylactic antibacterial regimens administered to premature infants in the first 5 days of life. Infants who received penicillin and sulfisoxazole (Gantrisin) were observed to have a higher incidence of kernicterus at autopsy than those who received oxytetracycline (Terramycin). The fate of the survivors of this tral has been of great interest and is the subject of the present report.

SUBJECTS AND METHODS

The survivors of the antibacterial prophylaxis trial were contacted by a proctor at frequent intervals following their discharge from the premature nursery to vouchsafe their appearance at a planned follow-up examination. Sixty-six individuals appeared for follow-up examinations (Fig. 1). As can be seen in Table I, the infants who returned for examination were not essentially different from those who failed to return and represented a reasonable sample of the survivors. A series of appointments for examination were arranged for each infant at the time of his second birthday (±2 weeks). The examinations were performed by the evaluators in the presence of the mother and the proctor. The evaluators were permitted to know only that the subjects were 2 years of age. The proctor instructed each mother not to reveal any interval history or other possible identifying data until the examination was completed and a categorical diagnosis was recorded upon appropriate forms. Following this, the evaluator was permitted to read a complete nursery and interval history and to question the mother fully. The child was then re-examined or re-evaluated as indicated in the light of the historical details, and the evaluator then recorded his "unmasked" diagnosis upon a second form.

The following examinations were performed under the restrictions described above: (1) neurologic examination; (2) psychometric examination; (3) language and speech evaluation; (4) dental examination; (5) complete physical examination; (6) audiometric examination; (7) ophthalmologic examination; (8) electroencephalogram.

Only in the results of examinations 1 to 4 were abnormal findings revealed often enough to warrant analysis in this report. Therefore, no

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further reference to the results of the last 4 examinations (supra) will be made.

TABLE I. COMPOSITION OF THE SAMPLE OF INFANTS WHO RETURNED VERSUS THOSE WHO DID NOT RETURN FOR FOLLOW-UP EXAMINATION*

	OXYTETRACYCLINE		PENICILLIN/SULFISOXAZOLE	
	FOLLOW-UP (47)	NO FOLLOW-UP (18)	FOLLOW-UP (19)	NO FOLLOW-UP (14)
birthweight, mean (Gm.)	1,564	1,666	1,609	1,593
standard deviation (Gm.)	±290	±210	±213	±240
male:female	24:23	9:9	9:10	6:8
white:nonwhite	34:13	12:6	10:9	8:6
private:ward	25:22	2:16	6:13	4:10
pelvic:cesarean	43:4	17:1	16:3	14:0
cephalic:breech	32:11	14:3	13:3	12:2

*Except for over-representation of "private" service children in the oxytetracycline follow-up group, there was no essential difference in the composition of the groups of infants who returned for follow-up examination and those who refused to return or could not be located.

The neurologic examination included an appraisal of activity, gait, speech, cranial nerves, motor and cerebellar function, sensation, and deep and superficial reflexes. At the conclusion of the examination the neurologist classified each child as follows: (1) no definite evidence of neurologic deficit; (2) abnormality on examination (i.e., overactivity, walking on toes, eversion of feet, etc.) not suggestive of neurologic deficit; (3) suspicious evidence of neurologic deficit; (4) definite evidence of neurologic deficit.

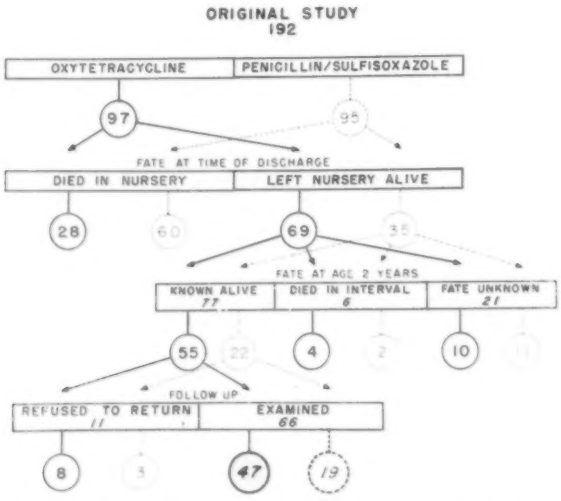

Fig. 1.—Sixty-six individuals (47 who had been in the oxytetracycline group and 19 who had been in the penicillin/sulfisoxazole group) returned for follow-up examinations at 2 years of age.

Psychometric evaluation consisted of observing the child's performance and comparing it with Gesell Developmental Schedules. The following categorizations were made: (1) defective,

≦16.5 months (developmental age); (2) borderline, 16.6 to 19.5 months; (3) dull average, 19.6 to 22.5 months; (4) average or above, ≧22.6 months.

Language and speech evaluation consisted of appraising the child's ability to respond to auditory, visual and tactile stimuli, and his ability to communicate. The total developmental landmarks in all areas of peripheral and central language functions were included (i.e., sense perception, symbol behavior, perceptual functions, hand-eye coordination, body identification, etc.). Language and speech development was classified as "adequate" or "retarded." In addition, the examiner made an attempt to identify "organic" responses when the language profile or the behavior pattern suggested a deficit in the central nervous system. This arbitrary diagnosis was labeled "organicity."

Dental examination was performed to establish the presence of enamel aplasia. A diagnosis was made if a clearly visible defect was observed in the crown of one or more of the teeth present.

In all analyses of the evaluations to follow, only the "masked" diagnoses (i.e., before the historical data were disclosed) will be considered. It is of interest to note in passing that only rarely did the evaluators record a second (different) diagnosis after the historical details were revealed.

The independent diagnoses assigned to each child by the evaluators corresponded surprisingly well. The diagnoses were arbitrarily classified as "normal" and "abnormal" and then correlated (Table II). In all except the "speech versus dental" comparison, associations were demonstrated which would be expected to occur infrequently as the result of chance alone.

TABLE II*

		PSYCHOMETRIC		SPEECH		DENTAL	
		N	Abn	N	Abn	N	Abn
Neurologic	N	36	5	24	22	36	9
	Abn	2	11	1	13	7	7
		$\chi^2 = 17.449$		$\chi^2 = 7.198$		$\chi^2 = 4.097$	
		$p < 0.01$		$p < 0.01$		$p < 0.05$	
Psychometric	N			23	17	32	6
	Abn			1	16	9	8
				$\chi^2 = 11.007$		$\chi^2 = 4.779$	
				$p < 0.01$		$p < 0.05$	
Speech	N					19	7
	Abn					27	10
						$p > 0.05$	

Neurologic: N = no neurologic deficit, abnormality not suggestive of neurologic deficit.
Abn = suspicious and definitive evidence of neurologic deficit.

Psychometric: N = dull average or better.
Abn = borderline or poorer.

Speech: N = adequate speech.
Abn = retarded speech.

Dental: N = no aplastic enamel.
Abn = aplastic enamel.

*The independent diagnoses were observed to correlate with a frequency which would be expected to occur infrequently as the result of chance alone in all except the speech versus dental comparisons.

The proportion of survivors with neurologic deficit in the oxytetracycline group was practically identical with that observed among the penicillin/sulfisoxazole survivors (Fig. 2). Among 44 survivors in the oxytetracycline group who were examined, 7 were adjudged to have a neurologic deficit as manifested by hemiparesis in 2, spastic quadriplegia in 2, spastic diplegia in one child, monoparesis and broad-based gait in one, and hearing loss, extraocular muscle weakness, and limited and awkward use of the extremities in another. Three survivors in this group had suspicious evidence of neurologic deficit as evidenced by nystagmus and broad-based gait in one, genu recurvatum and abnormal planter reflexes in one individual, and dragging of one leg and broad-based gait in another.

Among 17 survivors in the penicillin/sulfisoxazole group who were examined, 2 exhibited signs of neurologic deficit, which were hemiparesis in one and gait disturbance and inequality of deep reflexes in another individual. Two manifested signs that were interpreted as suspicious evidence of neurologic deficit, which were ataxic gait and awkward use of the hands in one child and hyperactivity and awkward use of the hands in another. Seven of the survivors in the oxytetracycline group exhibited patterns of behavior or gait which were considered to be abnormal, but in the opinion of the neurologist these variations did not appear to indicate the presence of a neurologic deficit. Some individuals in this category were thought to be suffering from emotional disorders. Others with gait disturbances were considered to have minor orthopedic problems unrelated to a disorder of the nervous system. Six individuals in the penicillin/sulfisoxazole category were classified in this "abnormality no deficit" category.

After psychometric examination, a higher proportion of individuals in the oxytetracycline group were placed in the "borderline and defective" class (14/39) than was observed in the penicillin/sulfisoxazole group (3/18) (Fig. 3).

Language and speech revealed essentially the same proportion in each group of children who were judged to have retarded speech (oxytetracycline, 25/46; penicillin/sulfisoxazole, 12/19) (Fig. 4). A slightly lower proportion of the oxytetracycline survivors exhibited speech and behavior patterns that were interpreted as "organic" (oxytetracycline, 24/46; penicillin/sulfisoxazole, 13/19).

A slightly higher proportion of the oxytetracycline survivors had aplastic enamel on dental examination (oxytetracycline, 13/45; penicillin/sulfisoxazole, 4/19) (Fig. 5).

DISCUSSION

The neonatal experience of the original group of 192 premature infants in this study was startling. In the course of an evaluation of the effectiveness of two antibacterial drug regimens, we came upon an unexpected association between penicillin/sulfisoxazole treatment and high mortality. The high incidence of kernicterus observed at autopsy among the infants who received this treatment was equally disturbing and provocative.

The question of what happened to the brains of those who did not die seemed important to answer. The clinical recognition of all but the most severe grades of brain damage was so difficult in these premature infants during the neonatal period

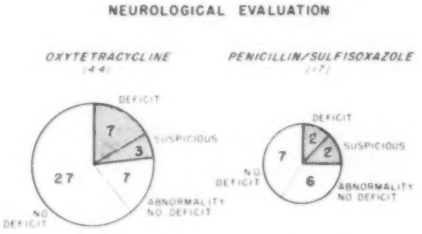

Fig. 2.—The proportion of survivors who were judged to have definite and suspicious evidence of neurologic deficit was essentially the same in the two groups (7 + 3/44 oxytetracycline; 2 + 2/17 penicillin/sulfisoxazole).

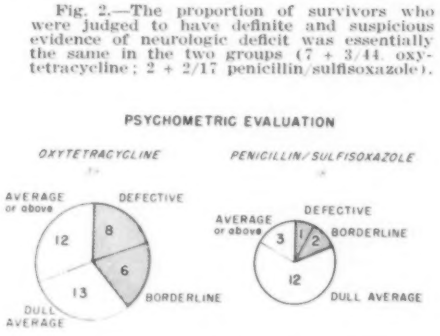

Fig 3.—A higher proportion of survivors in the oxytetracycline group was classified as defective and of borderline intelligence (8 + 6/39) than among the penicillin/sulfisoxazole survivors (1 + 2/18).

that it was impossible to estimate the number of survivors whose brain tissue had suffered. Our effort to make this estimate at 2 years of age indicates that the incidence of brain damage among a sample of the survivors of the penicillin/sulfisoxazole group, as judged by neurologic deficit, mental retardation, retarded speech, and dental enamel aplasia, was not significantly greater than that observed among the sampled oxytetracycline survivors.

This observation is interpreted to indicate that the neonatal mortality rate of this type of kernicterus in premature infants had been extremely high. The mortality rate among infants with kernicterus associated with Rh isoimmunization

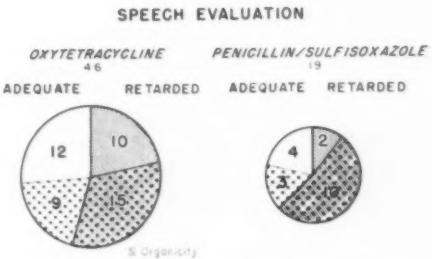

Fig. 4.—Essentially the same proportion in each group was judged to exhibit retarded speech, the number of individuals in the shaded areas (25/46, oxytetracycline; 12/19, penicillin/sulfisoxazole). As depicted in the stippled areas, a somewhat lower proportion (24/46) of the survivors in the oxytetracycline group manifested behavior and speech patterns that were thought to be "organic" when compared with survivors in the penicillin-sulfisoxazole group (13/19).

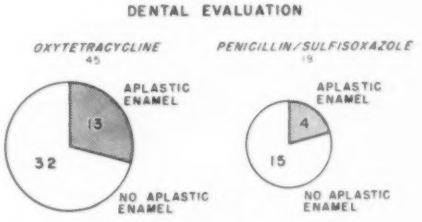

Fig. 5.—Aplastic dental enamel was observed slightly more frequently among the oxytetracycline survivors (13/45) than among the children who had received penicillin/sulfisoxazole (4/19).

was variously estimated in the era before the advent of exchange transfusion. Claireaux[2] reported that 33 of 37 infants died within two weeks after birth. Gerrard[3] observed that 37 of 78 infants with kernicterus died within the first month of life, an additional 10 died before reaching the age of 3 years. A high neonatal mortality rate has been reported among

premature infants who developed kernicterus in association with excessive doses of vitamin K analogues.[4] It is difficult to compare our experience with that of others because the diagnosis among those who survived is uncertain. It was our impression that very few of the infants who exhibited the typical signs of kernicterus (opisthotonus, rigidity, bradypnea, etc.) survived the first month of life. Some infants exhibited equivocal signs, and it was the borderline group of infants that made an accurate estimate of mortality rate impossible.

The fate of survivors of kernicterus associated with Rh isoimmunization has been reviewed in detail by Gerrard. Although severity of damage is not uniform, a high incidence of rigidity, choreoathetoid movements, mental retardation, and perceptive deafness has been described, and most of these signs were recognizable at 2 years of age. Among our survivors there were many examples of brain damage but none were thought to have clear-cut choreoathetosis, and perceptive deafness was noted infrequently (one example was recognized in the oxytetracycline group). Gerver and Day[5] demonstrated that the survivors of erythroblastosis fetalis (excluding those with obvious brain damage) had significantly lower intelligence quotients (Stanford-Binet) than their older unaffected siblings. These authors cited their observations as evidence that brain damage in erythroblastosis was not an all or none (fatal kernicterus or unaffected) phenomenon. The mean age of their survivors at the time of examination was 4½ years. Our children were examined at an earlier age and with a less exact test of intelligence. It is possible that re-examination of our subjects at a later age will also uncover evidence of more subtle damage among the penicillin/sulfisoxazole survivors. However, the data as they are here presented are consistent with the hypothesis that this type of kernicterus, if it occurs at all, is so severe that it causes death. As a result, the survivors would not be expected to show an unduly great incidence of brain damage.

A disturbingly high proportion (approximately one quarter) of these survivors of premature birth exhibited signs of neurologic deficit and mental retardation at the age of 2 years. This finding strongly suggests that the problem of brain damage among premature infants is one which requires at least equal consideration with the problem of reducing the mortality rate among these newborn infants.

SUMMARY

Though a high over-all incidence of brain damage was observed in a sample of 2-year-old children who had survived premature birth, the incidence of brain damage among those who had received penicillin/sulfisoxazole during the first 5 days of life was not significantly higher than that observed among others who had received oxytetracycline. It is implied from these observations that few, if any, infants survived the brain damage associated with penicillin/sulfisoxazole administration in the neonatal period.

Neurologic examinations were performed by Dr. Elizabeth Decker, Dr. Julia Schneider, Dr. Isabelle Rapin, and Dr. Sidney Carter;

language and speech evaluation by Mrs. Shulamith Kastein; psychometric testing by Mr. Adam Munz; dental examinations by Dr. Solomon N. Rosenstein; electroencephalogram interpretation by Dr. Eli S. Goldensohn; hearing evaluations by Miss Sylvia Morgan and Mr. Maurice Miller; ophthalmological examinations by Dr. George R. Merriam, Jr.; physical examinations by Dr. Beverly Morgan and Dr. Jack G. Shiller.

I wish to thank these collaborators for their cooperation and particularly for their patience in carrying out the terms of the "blind" examinations. I am indebted to Mrs. Thelma Phelan, the proctor, for her devoted and faithful efforts.

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HEMOGLOBIN METABOLISM IN THE PREMATURE INFANT

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THE premature infant commonly develops an anemia during the first few months of life. The subject has been intensively studied in the past and many mechanisms have been suggested, but two recent studies have contributed greatly to our understanding. Schulman, Smith, and Stern[1] emphasized the changes in total circulating fetal and adult hemoglobin that followed birth. Gairdner, Marks, and Roscoe[2] studied hematopoietic activity as revealed by serial bone marrow aspirations and related this to the hemoglobin concentration. Both groups agreed that a reduced rate of hemoglobin synthesis and the rapid growth of the premature infant were the major factors in causing the anemia.

The administration of glycine containing N^{15}, a nonradioactive isotope of nitrogen, results in the incorporation of the isotope into the hemoglobin.[3-5] This has made it possible to study the life span of the red blood cell and other aspects of hemoglobin metabolism. We have used this technique to study the mechanism of the anemia of prematurity in three infants.

Ammonium-N^{15} chloride was administered to one infant and glycine-N^{15} to two infants. The ammonium-N^{15} chloride was used because of its ready availability and because previous investigations in this laboratory have indicated that simple nitrogenous compounds may be incorporated into protein by infants.[6]

CLINICAL PROCEDURES

Infant ROM had a birth weight of 1,840 grams and was fed 770 mg. of ammonium-N^{15} chloride (95 atom per cent excess*) from the fifth to twenty-fourth hours of life. Seven milliliters of blood were withdrawn for analysis during the 4-month period of observation.

Infant ROD had a birth weight of 1,740 grams and was fed 2.0 Gm. of glycine-N^{15} (10 atom per cent excess) from the seventh to forty-eighth hours of life. The total amount of blood drawn for analysis over the 4-month period of observation was 14 ml.

Infant TOR had a birth weight of 1,750 grams and was fed 1.7 Gm. of glycine-N^{15} (10 atom per cent excess) from the fifth to forty-eighth hours of life. Thirteen milliliters of blood were withdrawn during the 110 days of observation.

The course of all infants was clinically uncomplicated except for an iron-deficiency anemia in infant ROD.

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*Obtained from Isomet Corporation, Palisades Park, N. J.

METHODS

Blood from a heel puncture was collected into a heparinized tube. The blood was centrifuged and the plasma removed. The red blood cells were washed three times with isotonic saline. The cells were mixed with an equal volume of distilled water and 0.4 volume of toluene, and the mixture was placed in the refrigerator overnight. The clear hemoglobin solution was removed with a pipette, and to this was added 10 per cent trichloroacetic acid. The precipitate was washed three times with 5 per cent trichloroacetic acid, dissolved in IN-NaOH, reprecipitated, and redissolved. The protein was then digested and the N^{15} content determined with a Consolidated Nier model No. 21-201 ratio mass spectrometer.[7]

The hemoglobin concentration was determined in a Klett colorimeter on blood hemolyzed in water. The instrument was standardized against a sample analyzed by oxygen capacity. The blood volume was calculated by body weight according to the data of Schulman and others.[1] The total circulating hemoglobin was calculated from hemoglobin concentration and blood volume. The total hemoglobin-N^{15} was derived from the N^{15} concentration and the total circulating hemoglobin.

Glycine-N^{15} was synthesized according to the method of Schoenheimer and Ratner.[8]

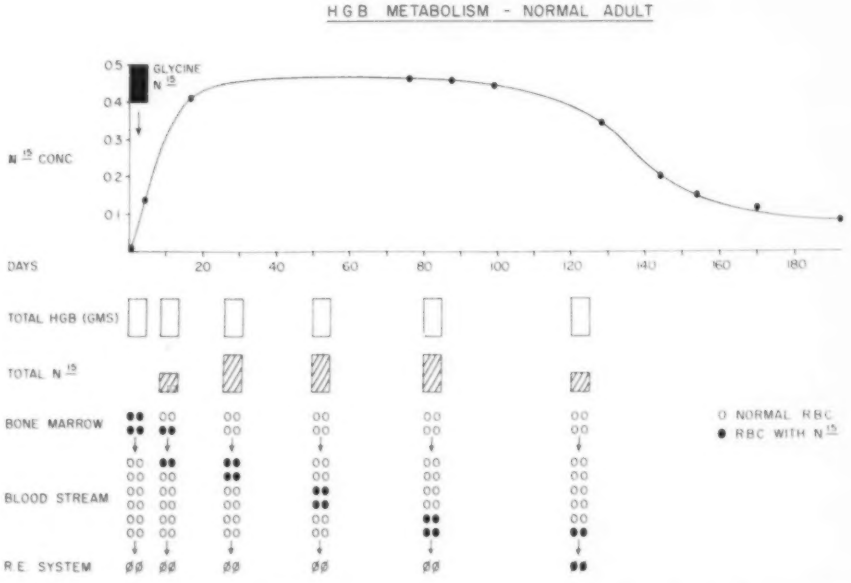

Fig. 1.—Hemoglobin-N^{15} concentration in normal adult after administration of glycine-N^{15} (after the data of Shemin and Rittenberg[4]). The factors producing the curve are presented schematically. Unlabeled red blood cells are empty circles; N^{15} red blood cells are filled-in circles. Total hemoglobin and total hemoglobin-N^{15} were calculated by multiplying the respective concentrations by the estimated blood volume.

THEORETICAL CONSIDERATIONS

In Fig. 1 is presented schematically the course of events in a normal adult following the administration of N^{15} glycine, based on the data of Shemin and Rittenberg.[4] During the administration of glycine-N^{15}, the cells undergoing synthesis in the bone marrow are labeled with N^{15}. As they appear in the blood stream, the N^{15} concentration of circulating hemoglobin rises. It then remains level as long as the rate of synthesis of new unlabeled cells is equal to the rate of degradation of old unlabeled cells. The N^{15} concentration gradually decreases as the tagged cells reach the end of their life span and are degraded. Few cells are degraded in less than 40 days, and the average life span is 110 to 130 days.[4, 5] The N^{15} concentration falls off in an S-shaped curve, probably because of reutilization of N^{15} released from degraded hemoglobin and other proteins. This probably also explains the slight convexity seen during the "plateau" period in some instances.

In Fig. 2 are presented the changes that might be expected from an alteration in the rate of synthesis after the tagged cells have entered the blood stream. Although the total circulating N^{15} remains unchanged, the concentration rises if the rate of synthesis falls and falls as the rate of synthesis increases. The total hemoglobin and hemoglobin concentration also change.

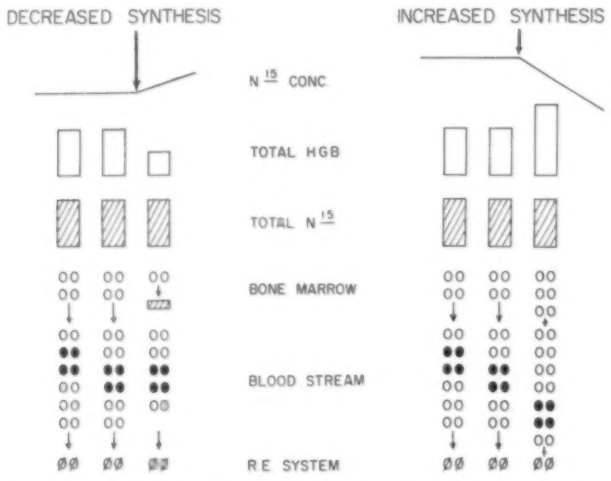

Fig. 2.—The expected effect on hemoglobin-N^{15} of a change in rate of synthesis of red blood cells (see text and Fig. 1 for explanation).

If, following the entry of tagged cells into the blood stream, the life span of the circulating cells was suddenly shortened, the N^{15} concentration of the circulating hemoglobin would rise and the total N^{15} would be unchanged (Fig. 3). If, however, a hemolytic crisis was to strike cells at random, the total N^{15} would fall but the N^{15} concentration would remain the same.

RESULTS

With this theoretical introduction, we can inspect in detail the data from infant ROM (Fig. 4). The hemoglobin concentration (bottom line) fell from 17.3 Gm. per cent on the sixth day of life to 9.9 Gm. per cent on the fifty-second day and then

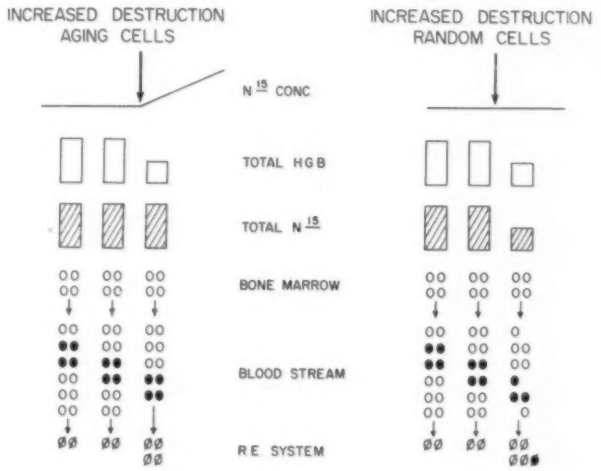

Fig. 3.—The expected effect on hemoglobin-N^{15} of an increased rate of destruction of red blood cells (see text and Fig. 1 for explanation).

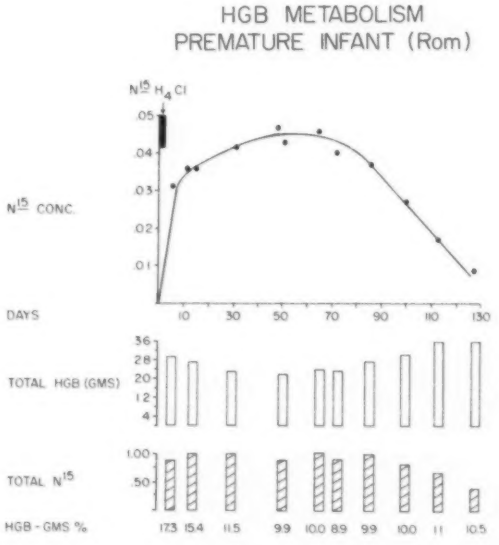

Fig. 4.—Premature infant ROM, presenting an uncomplicated course of anemia of prematurity.

remained around 10 Gm. per cent for the rest of the observation period. This is a common clinical course in the premature infant. In examining the rest of the data, it is evident that several different stages enter into this simple course. During the first 6 days, the N^{15} concentration of the circulating hemoglobin rose rapidly as the newly labeled cells entered the circulation. A second phase extends from 6 to 50 days in which the N^{15} concentration continued to rise slowly but the total hemoglobin-N^{15} remained stable and the total hemoglobin fell. This conforms with the changes expected from a reduced rate of synthesis. From 50 to 70 days the curve resembles the plateau in the adult, with the rate of synthesis equal to the rate of degradation. This is followed by the next phase (70 to 90 days) during which the N^{15} concentration fell although the total N^{15} remained constant and the total hemoglobin rose. During this period, the rate of synthesis exceeded that of degradation but the hemoglobin concentration remained unchanged because of the rapidly increasing blood volume caused by the growth of the infant. And finally, some time after the eighty-fifth day, the total N^{15} began to fall, indicating beginning death of

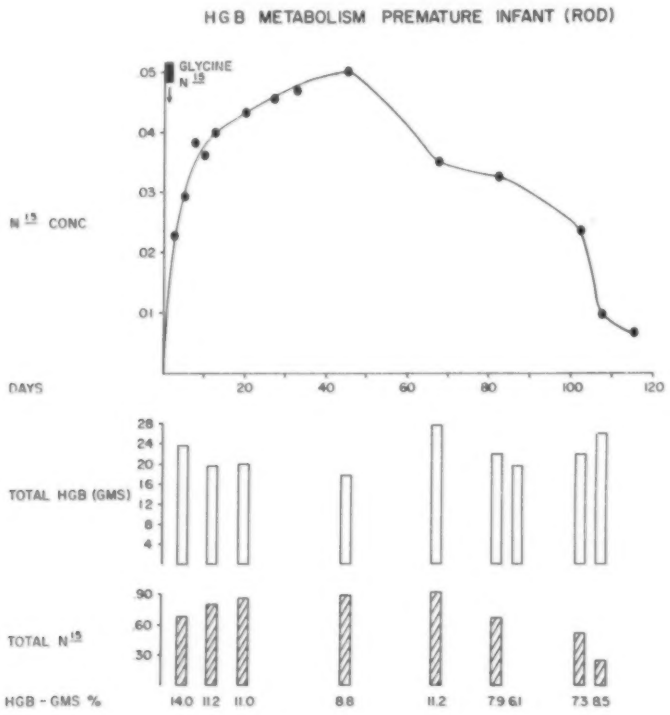

Fig. 5.—Premature infant ROD, iron-deficiency anemia in the third month follows the early anemia of prematurity.

the tagged cells. About one half of the tagged cells had left the circulation by the one-hundred-twentieth day.

The course of infant ROD (Fig. 5) up to the seventieth day of life was similar. During the first 10 days there was a rapid increase in the concentration of N^{15} as the tagged cells entered the circulation. This was followed by a slow rise during the tenth to forty-fifth days and accompanied by a fall in the total hemoglobin and hemoglobin concentration and a constant total N^{15}. This is the picture that would be expected from a decrease in the rate of synthesis. Between the forty-fifth and sixty-eighth days there was an abrupt drop in the N^{15} concentration as the rate of synthesis rapidly increased. The total hemoglobin and hemoglobin concentration increased and the total N^{15} remained constant.

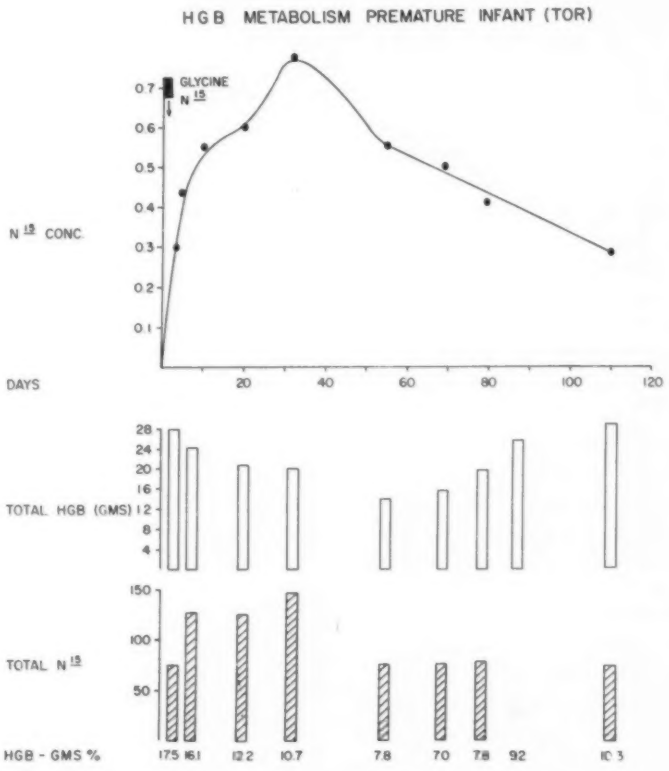

Fig. 6.—Premature infant TOR, an acute hemolytic episode in the second month complicates the typical picture.

On the eighty-second day of life, the infant again developed an anemia, and it was discovered that the mother had not been administering iron supplements. On reinstitution of medication, there was a rapid rise in

hemoglobin concentration. The iron-deficiency anemia complicates the N^{15} picture and permits more than one interpretation of the data. We shall present the interpretation that appears most likely, taking all factors into consideration. The total N^{15} began to fall after the seventieth day and about one half of the tagged cells had disappeared by the one-hundred-fifth day. This conforms to the normal life span of the tagged cells as seen in infant ROM and that reported for adults. Despite the fall in total N^{15}, there is a flattening in the curve of N^{15} concentration at the time when the hemoglobin concentration and total hemoglobin were falling. This could result from a decrease in the rate of synthesis resulting from the iron deficiency. Finally, the N^{15} concentration fell precipitously, probably reflecting the combined effects of increased synthesis and the death of the tagged cells.

The course of infant TOR (Fig. 6) was, by conventional methods of study, not unusual. There was a gradual fall in hemoglobin concentration and total hemoglobin during the first 70 days of life, followed by a gradual recovery. However, the N^{15} curve is unusual and provocative. The first two phases of the curve of N^{15} concentration follow the expected pattern: a rapid increase during the first 10 days, followed by a more gradual rise up to the thirty-fifth day. However, between the thirty-fifth and fifty-second day there was an abrupt fall in the concentration accompanied by a fall in the total N^{15} and a continuing fall in the total hemoglobin. This suggests a hemolytic crisis affecting cells at random and associated with increased compensatory synthetic activity (to account for the lower concentration of N^{15}) or a hemolytic crisis affecting preferentially the tagged cells. The latter explanation is suggested by the fact that the N^{15} concentration fell more sharply than the hemoglobin concentration. However, since only two observations of hemoglobin and N^{15} are involved, it would be dangerous to accept this conclusion. Following this, the N^{15} concentration continued to fall while the total hemoglobin rose and the total N^{15} remained stable in the pattern associated with increased synthesis. There was no further drop in the total N^{15} during the 115 days of observation, possibly because of the previous hemolytic crisis.

The constancy of total N^{15} during the latter half of the curve is unexpected and invites some speculation. It has been reported that the older red blood cell differs metabolically from the younger and is more susceptible to certain hemolytic agents.[9] In this instance it is possible the labeled cells that were destroyed in the hemolytic episode consisted largely of the population that normally would be destroyed first, between 80 and 120 days. Another factor that could contribute to maintaining the circulating N^{15} level would be reutilization of the N^{15} released by the destroyed cells. The synthesis of new red blood cells has probably begun by this time, making this possible.

SUMMARY AND CONCLUSION

1. N^{15} was administered to 3 premature infants. The hemoglobin concentration and the N^{15} concentration in the hemoglobin were followed. The

total circulating hemoglobin and the total N^{15} in hemoglobin were calculated using average figures for the blood volume. The following pattern was observed:

Phase 1, first 6 to 10 days, the N^{15} concentration rose rapidly as newly synthesized red blood cells containing N^{15} appeared in the circulation.

Phase 2, from 10 to 50 days, the N^{15} concentration rose more slowly while the total circulating N^{15} remained constant and the total circulating hemoglobin fell. In this period the rate of synthesis had slowed.

Phase 3, 50 to 80 days, the N^{15} concentration began to fall while the total circulating N^{15} remained constant and the total hemoglobin began to rise. This corresponds to a period of increased synthetic activity.

Phase 4, 80 to 130 days, the N^{15} concentration continued to fall and the total hemoglobin to rise but the total circulating N^{15} began to fall. During this period rapid synthesis of new cells continued and the tagged cells began to reach the end of their life span.

It is concluded that the anemia of prematurity results from a decreased rate of synthesis, the effects of which are exaggerated by the rapid growth of the infant and the increase in blood volume. The red blood cells have a normal life span.

2. In one infant an iron-deficiency anemia occurred after the eightieth day of life. The changes in N^{15} concentration indicated a slowing in rate of synthesis.

3. In another infant there was an abrupt drop in total circulating N^{15} about the sixtieth day of life, suggesting a hemolytic crisis. This occurred in the absence of clinical signs and would not have been detected by conventional methods of study.

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LACTIC ACID MILK IN THE FEEDING OF PREMATURE INFANTS

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MANY virtues have been ascribed to acid milks.[1] Initially it was observed that infants seemed to thrive better on buttermilk than on ordinary sweet milk, and other sour milk formulas were soon introduced. Marriott[2, 3] initially recommended sour milk only for sick infants (1919), but later used it as a routine feeding for healthy infants (1923). He concluded that it diminished the work of digestion by entering the stomach at the desired pH, whereas sweet milk had to be reduced to an optimal pH by hydrochloric acid in the gastric juice. He also advocated acid milk for its bactericidal action against dysentery and typhoid organisms (1927).[4]

Brennemann[5] and others[6] believed that the principal value of acid milk for infant's formulas was in the finer consistency and lesser toughness of its curd in contrast to that of sweet milk.

Other authors have attributed such beneficial factors to sour milk as enhanced absorption of fat, iron, calcium, and phosphorous, increased resistance to intestinal and parenteral infections, and acceleration of recovery from illness.[7-16] Blue and Davison[17] have used lactic acid milk routinely for the past 25 years in the nurseries of Duke University Hospital, preferring it because of its "bactericidal activity" and its sterility.[18, 19]

The addition of lactic acid to cow's milk is also supposed to reduce the allergenicity of its protein. For example, in 5 infants who developed bloody diarrhea while receiving cow's milk, normal stools followed acidification of the formula with one teaspoonful of U.S.P. lactic acid to each pint of formula.[20]

In view of these apparent advantages of acidified milk and because of the frequent low blood calcium levels and the susceptibility to infection and the deficient fat absorption in premature infants, it seemed desirable to determine if lactic acid milk might have advantages for them. Therefore, the present study was designed to compare the efficiency of lactic acid milk (Pelargon*) as a feeding for premature infants with that of two standard milk feedings, one relatively high in protein and low in fat (Alacta†) and the other an evaporated cow's milk formula (E.M.‡).

MATERIAL AND METHODS

Infants.—Forty-four premature infants in the Premature Unit of The

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This study was aided by a grant from the Nestlé Company, White Plains, N. Y.

*Pelargon was supplied by the Nestlé Company, White Plains, N. Y.

†Alacta and Dextri-Maltose No. 1 (new) were supplied by the Mead Johnson Company, Evansville, Ind.

‡Evaporated milk was supplied by the Pet Milk Company, St. Louis, Mo.

Long Island Jewish Hospital during the period from Aug. 18, 1956, to June 19, 1957, comprised the study group. The birth weights of the infants ranged from 1,417 to 1,800 grams. They were either born at the hospital or transported to the hospital before their fourth day of life by the Premature Transport Service of New York City.

Feeding Routine.—Newborn infants were fed nothing by mouth for 24 hours, or longer, as conditions warranted. Milk feedings were increased gradually and by the tenth day of life the infants were receiving isocalorie feedings of 114 calories (mean) in 143 ml. of liquid (mean) per kilogram of body weight per day. Isocalorie feedings were maintained by readjusting the volume of the milk intake thrice weekly at the same hour, according to the weight changes of the infants.

TABLE I. CHEMICAL COMPOSITION OF MILKS AFTER PREPARATION (GRAMS PER 100 ML.)

	CALORIES PER OUNCE	PROTEIN	FAT	CARBOHYDRATE	ASH
Alacta	24	3.86	1.40	13.0	0.82
Evaporated milk	23	2.73	3.08	9.50	0.59
Pelargon	24	3.33	3.50	9.01	0.75

Milk Formulas

1. High protein—low fat milk consisting of half skimmed cow's milk with added carbohydrate (Alacta)
   Preparation: 454 Gm. of Alacta powder and 585 ml. of 50 per cent dextri-maltose solution diluted to 3,880 ml. with water
   Calories: 0.8 per ml.; 24 per ounce
2. Evaporated milk with added carbohydrate
   Preparation: 390 ml. of milk and 114 ml. of 50 per cent dextri-maltose solution diluted to 1,000 ml. with water
   Calories: 0.77 per ml.; 23.1 per ounce
   Fifty per cent dextri-maltose solution was prepared by dissolving 454 Gm. of Dextri-Maltose No. 1 (new) in water and diluted up to 908 ml. with additional water
3. Lactic acid–evaporated milk mixture (Pelargon)
   Preparation: 227 Gm. of Pelargon powder diluted to 1,300 ml. with water
   Calories: 0.8 per ml.; 24 per ounce
   Lactic acid 2.2 per cent
   After preparation, the formula had 0.4 per cent of a racemic mixture of lactic acid, half of which was levorotatory and half, dextrorotatory

The infants were placed in one of three feeding groups on a random-rotation basis: (1) Alacta, (2) Pelargon, and (3) evaporated milk. An attempt was made to have an equal number of infants in each group. Infants were excluded from the study if they were (1) under 1,400 grams or over 1,800 grams at birth, (2) in poor condition during the first 7 days of life, or (3) seriously ill during the course of study (Table I).

The caloric values of the feedings were calculated from the data supplied by the manufacturers of each milk product and the exact volume of intake of each infant per feeding was recorded. The nursing staff made an exceptional effort to ensure the ingestion of the prescribed volume of milk by each infant whether tube fed or nipple fed.

TABLE II

COLOR AND SEX	AVERAGE GAIN (GM./ KG./ DAY)	INTAKE OF CALORIES (CAL./ KG./ DAY)	BIRTH WEIGHT	WEIGHT AT 10 DAYS
High Protein–Low Fat Milk (Alacta)				
W—M	5.9	113	1,758	1,848
W—F	20.6	114	1,531	1,474
W—M	13.4	118	1,588	1,390
W—F	11.3	118	1,729	1,760
W—F	12.6	117	1,673	1,673
W—F	12.3	112	1,758	1,594
W—F	12.9	118	1,729	1,630
W—M	18.1	122	1,588	1,539
W—F	13.7	108	1,602	1,559
N—M	22.6	102	1,559	1,531
W—M	19.5	103	1,616	1,545
W—M	19.0	108	1,758	1,743
W—M	15.5	107	1,616	1,420
W—F	15.3	113	1,630	1,588
W—F	14.9	110	1,503	1,580
W—M	14.9	115	1,460	1,389
N—M	12.6	124	1,417	1,305
W—M	19.1	114	1,715	1,701
Total of 18 cases	15.2	113	1,624	1,571
Lactic Acid Milk (Pelargon)				
W—F	10.4	117	1,474	1,403
W—F	9.3	118	1,701	1,602
Y—F	11.0	121	1,786	1,810
W—F	10.6	118	1,559	1,354
W—M	10.7	116	1,701	1,400
W—F	13.3	119	1,710	1,660
W—M	10.3	118	1,644	1,536
N—M	12.1	119	1,474	1,353
W—F	12.9	119	1,673	1,467
W—F	14.6	116	1,673	1,559
W—M	9.8	112	1,729	1,773
W—M	13.1	119	1,588	1,536
N—M	14.6	120	1,531	1,450
N—M	12.8	109	1,474	1,604
Total of 14 cases	11.8	117	1,623	1,536
Evaporated Milk				
W—F	14.8	119	1,770	1,517
N—M	15.8	116	1,727	1,751
W—F	24.6	113	1,545	1,723
W—F	16.8	116	1,588	1,373
N—M	11.0	115	1,729	1,680
W—F	17.7	113	1,758	1,580
W—F	11.7	112	1,800	1,680
W—M	13.2	104	1,602	1,334
W—F	18.3	115	1,588	1,830
N—F	14.3	115	1,417	1,300
W—M	21.0	105	1,559	1,546
W—M	20.6	111	1,446	1,478
Total of 12 cases	16.6	113	1,627	1,566

RESULTS

The data were analyzed for differences between Negro and white infants, between males and females, between multiple and single births, between transport and nontransport cases, and between tube-fed and nipple-fed infants. No significant differences were found. The mean birth weight of the entire group was 1,625 grams and the mean weight gain was 14.5 grams per kilogram per day.

The mean gain in weight in grams per kilogram of body weight per day was calculated by the formula described by Kagan and co-workers[21]; however, the period of observation in this study was from 10 days of age to the day of achieving 2,000 grams instead of from 7 to 28 days as in Kagan and his associates' study.

The gains in weight of the premature infants who received lactic acid milk were 22.4 per cent less than those fed the high protein–low fat milk formula and 28.9 per cent less than those fed the evaporated milk and dextrimaltose mixture. The average weight gains in grams per kilogram per day were: lactic acid milk, 11.8; high protein–low fat milk, 15.2; evaporated milk, 16.6 (Table II).

This relatively lower gain in weight occurred even though the infants on lactic acid milk received a mean daily calorie intake of 117 calories per kilogram per day as compared with 113 for the infants who received Alacta and evaporated milk.

The incidence of morbidity was similar in all three groups except that in the Pelargon group there were 5 cases of oral thrush. Three infants on high protein, high ash, and low fat

milk (Alacta) had loose stools. Tetany was not observed in any of the infants of the three groups nor were other significant disturbances observed in any group (Table III).

One infant on lactic acid milk died on the thirty-first day of life and was excluded from the study. Her birth weight was 1,162 grams. On the twenty-third day of life she manifested apnea, cyanosis, lethargy, and anemia. The autopsy did not reveal the cause of death. Another infant who was receiving lactic acid milk was excluded from the study because at 18 days of age she had loose stools, a distended abdomen, and fever. *Klebsiella pneumoniae* and *Staphylococcus aureus* were cultured from the nose and throat. Lactic acid milk was discontinued and Alacta substituted. She recovered after 13 days of chloramphenicol therapy.

The nurses had difficulties with the lactic acid milk in tube feedings; the coarseness of the milk necessitated greater force to introduce it through the fine polyethylene tube. The nurses also observed pallor and "unhappy" facies in the infants receiving lactic acid milk after 5 to 7 days of such feeding.

DISCUSSION

Advocates of lactic acid milk based their recommendations for it partly on theoretical grounds and partly on clinical observations which indicated its superiority under the particular conditions of their investigations. Older literature concerned with infant feeding seems to have substantiated, in principal, the advantageous claims made for acidified milk.

Owing to the increased cleanliness in milk production and the wider use of pasteurization and refrigeration, diarrheal disorders have decreased sharply in infants fed cow's milk formulas. Thus, one of the reasons for which acidified milks were recommended has likewise been reduced.

The feeding of premature infants continues to pose problems, although to a lesser extent than was formerly the case. Infections are common. The blood calcium level is usually low,[22] the blood phosphorus high, and fat absorption is deficient as compared with the full-term baby. It was for these reasons that we attempted to determine whether lactic acid milk might be superior to other milks for the small premature infant.

TABLE III. MORBIDITY INCIDENCE (NUMBER OF CASES)

CONDITION	LACTIC ACID MILK	HIGH PROTEIN–LOW FAT MILK	EVAPORATED MILK
Oral moniliasis	5	0	1
Loose stools (no pathogens)	0	3	0
Nasal congestion	0	1	0
Skin pustules	1	0	0
Conjunctivitis	1	1	1
Total morbidity	7 (14)	5 (18)	2 (12)
Per cent morbidity	50	28	17

Our experience with lactic acid milk in the small premature infant weighing less than 1,800 grams indicates no superiority but definite inferiority in comparison with sweet milk. Infants fed lactic acid milk gained less weight, appeared pallid, and seemed discontented.

On numerous occasions we observed an increased gain in weight and a general well-being of the infants whose feeding was changed from acid milk to a sweet milk. The reverse was also true in most instances.

Infection was not appreciably different in the three groups, although oral infections with *Candida albicans* were predominant in the Pelargon group.

Passarino[23] gave lactic acid milk (Pelargon) to 33 premature infants and reported greater gains in weight than those reported here. Our studies are not comparable, however, since the premature infants in his study were generally larger and older, the caloric intake was higher (140 calories per kilogram per day), and the weight gains were not recorded in grams per unit of body weight. Jacobs and Christian[24] fed acidified milk (Pelargon) to 40 full-term newborn infants and observed satisfactory gains in weight from the second through the fourth weeks of life. It is possible that as the premature infant approaches the full-term infant in weight, surface area, and physiologic maturation he may tolerate acid milk and thrive on it.

Explanation for the poorer results in infants fed acidified milk led to several investigations. The possibility that these infants excreted more fat than the others was explored. It was found that they excreted about 1 Gm. of fat daily more than those on Alacta excreted and about the same as those on evaporated milk. We did not feel that this loss of fat was responsible for producing the poor results in lactic-acid milk-fed infants, since the mean caloric intake with Pelargon was 117 calories per kilogram per day and 113 with the other milks, and particularly since infants on evaporated milk with a similar loss of about 9 calories daily showed better results.

The possibility that acidosis resulted from the lactic acid milk was also explored; blood pH and carbon dioxide determinations demonstrated lowering of each. The nature of this acidosis, the reason for its occurrence, and the physiologic explanations for the poor weight gains are now under investigation. The results of these investigations will be the subject of Part II of this study.

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"Dear Sir: I have given you the history of that child so far as I know, except one fact; the father tells me to-day that when the child was born he was considered the biggest and finest boy that had been born in the community for a long time. . . ."

Lewis A. Sayre, M.D., from "On the Deleterious Results of a Narrow Prepuce and Preputial Adhesions," transactions of the Ninth International Medical Congress, 1887.

A REVIEW OF TWELVE CASES OF ENCOPRESIS

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THE purpose of this paper is to present a comparative study of twelve cases of fecal soiling followed at The Harriet Lane Home, Children's Psychiatric Service, during the year 1957 to 1958. Encopresis is seen predominantly in the pediatric age group. When encountered, it is frequently resistant to therapy. The experience gained in our treatment of these children has led us to view the problem with a more optimistic outlook.

The first recorded case of psychogenic fecal soiling was presented by Fowler[1] in 1882. Little interest was shown in this problem until Weissenberg[2] clarified the psychogenic and organic aspects of the symptom in 1926 and coined the term "encopresis," which denotes the act of involuntary defecation not directly due to organic causes.[3]

In 1938 Shirley[4] reviewed 70 cases of fecal soiling seen over the previous 7 years at The Harriet Lane Home, Children's Psychiatric Service. This represented an incidence of 3 per cent of the total admissions up to that date. Approximately one third of the patients had an I.Q. below 70, and this was felt to be a factor in the problem. In the group with I.Q.'s of above 70, the ratio of boys to girls was 4 to 1.

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In the natural history of the encopretic child, constipation with the development of megacolon is a frequent finding. This result frequently leads to an investigation to rule out the possibility of Hirschsprung's disease. Thus, in 1954 Richmond and associates[5] clearly differentiated between the psychological and organic factors in the development of megacolon. In the psychogenic type, fecal soiling is the major complaint; the onset occurring after neuromuscular control is gained is to be expected. Additional symptoms are as follows: infrequent use of the toilet for defecation, inhibition of stool, periodic voluminous stools, feces-packed rectum, the absence of a spastic segment of rectum or rectosigmoid on fluoroscopy, and a relatively benign course. On the other hand, patients with neurogenic megacolon (Hirschsprung's disease) present constipation or obstipation as the major complaint. The onset is at birth or in the first few weeks of life. Additional characteristics are as follows: fecal soiling usually not present, frequent episodes of intestinal obstruction, an empty rectum, presence of a spastic segment of rectum or rectosigmoid, and eventual death if untreated.

Anthony,[6] in a comprehensive paper published in 1957, divided encopresis into two types and substantiated his distinction by experimental method. The one type he termed

"continuous" on the basis that the symptom of soiling was present throughout the patient's early life. The second class termed "discontinuous" showed a period of freedom from symptoms following the completion of toilet training. Anthony reported the "continuous" child as a dirty child, from a dirty family, burdened with every conceivable sort of social problem. Associated factors are as follows: a high incidence of enuresis, low-pressure toilet training, low levels of maternal aspiration, marked social and emotional regression, obsessional traits frequently absent, child usually neglected or rejected, leakage symptoms prominent, child's reaction shameless, educational backwardness characteristic, and parents frequently psychopathic.

In contrast the "discontinuous" child was described as the compulsive child of a compulsive family. In this group associated factors are as follows: low incidence of enuresis, high-pressure toilet training, high levels of maternal aspirations, social and emotional regression less marked, obsessional traits frequently present, marked reactions of guilt and shame, child often overprotected, academic performance good, and parents frequently obsessional and emotionally inhibited.

The 12 cases in our series represented 6 per cent of the annual case load. There were 10 boys and 2 girls, ranging from 5 to 13 years of age. The group included one Negro child. The children were all of normal or superior intelligence as measured on the Stanford-Binet test. Duration of symptoms ranged from 3 weeks to 10 years. The majority had a history of longer than 2 years. Symptoms of less than 6 months' duration were arbitrarily termed as acute, and longer than 6 months as chronic. The onset, frequency, and duration of fecal soiling showed marked variability from case to case. Associated complaints included a wide range of childhood problems.

All were from homes in which a fair degree of economic and social stability was present. We did not have any case from the low-income dilapitated families such as would fall into Anthony's "continuous" class, although there are several cases of this nature on record in the files of previous years.

CASE REPORTS

CASE 1.—David S., when first seen, was a 7-year-old boy who had never been bowel trained to his mother's knowledge. He had received a thorough medical investigation in a northeastern medical center where, among other recommendations, psychotherapy was advised.

His problem had become the focus of attention of the household. By both parents it was viewed with disgust and resignation. His bathroom visits were an elaborate ritual in which he first announced to one and all that he was going to have a B.M. At the side of the toilet was a special towel and washcloth with which he cleaned himself following a movement and which was then placed in a special hamper. A freshly laundered pair of underclothes and pants were beside the toilet at all times, into which he dutifully changed at the end of each visit. If the sitting was successful, which was infrequent, his mother or father were called in to view the prize.

At intervals David would become impacted, throwing the family into a state of intense concern. In this event David allowed only his mother to give him an enema and only his favorite brother to hold the receptacle.

History revealed that following a difficult delivery Mrs. S. was told her son could be expected to die, to be normal, or to be mentally retarded. As a child David was described as clinging, and his mother was overprotective.

The father was a minister, a warm person but a rigid disciplinarian. The mother was a perfectionist about her household and her children's upbringing.

David was a thin, hyperactive, immature boy who achieved an I.Q. of 93. He was neat in his appearance and compulsive about his habits. In therapy he enjoyed drawing toilets with B. M. in them and would inevitably draw attention to the verdigris around the bolts at the base of the toilet. At times he liked to curl up in a cradle that was in the waiting room.

After 4½ months of therapy, David's bowel habits were unchanged, as were the family's attitudes. It was felt that without a change of environment, psychotherapy would be to no avail. He was placed in a rural convalescent hospital for children where after two months his soiling had decreased considerably.

CASE 2.—Damon L. was a 10-year-old boy who was brought for treatment with symptoms of fecal soiling and constipation of 8 years' duration. The boy had been investigated in military hospitals in Japan and America where organic causes had been ruled out. Mrs. L. could recall no time when he was free of symptoms. His early bowel training had been carried out by a grandmother and nursemaid while his mother worked. His birth history and development were essentially normal.

The father was an officer in the military service, who, because of the demands of his profession, was frequently away from home. The mother was an obsessive woman of an artistic temperament, who felt torn between her family and her art. She entertained considerable guilt feelings about sex and complained of some incompatibility with her husband.

Damon was a brilliant child who achieved an I.Q. of 162. His interests were wide and his knowledge remarkable. He was a compulsive boy with a detached attitude about his problem but was quite aware of the disgust and extra labor it caused his mother. He recalled with anxiety episodes of being "stopped-up" and told of the frequent need "to bear down, to see if it was working." His concept of his body was that of a cavity filling his entire trunk in which were deposited large clumps of B.M. By bearing down and pressing his forearm across his stomach, he could displace this mass. He was aware of parental discord, and one day he acted out a scene in which a woman murdered her husband. Their son discovered the crime and reported it to the police.

Under therapy, the parents' relationship improved and they in turn became more understanding of the boy.

Within 3 months following the onset of therapy, Damon gained control of his bowels. In times of stress his soiling would appear for short periods.

CASE 3.—Jane D. was a 9-year-old girl who was referred because of the daily staining of her underclothes for several years. Her accidents occurred mostly in the home. She had been free of symptoms for two weeks while away at a summer camp. The mother felt that Jane was a poor mixer and "off on cloud seven." Jane was continuously getting into fights with an older sister, usually coming off second best.

The night before her first visit to the clinic she typed a letter to her parents in which she asked, "Why do you love me, because I look so sick?" and ended by saying, "I hate Pat [the older sister] and that is for sure."

The father was a lawyer who suffered from migraine headaches. The mother was a highly trained comptometer operator before her marriage. She was a dynamic person who was able to recall, in detail, her daughter's bowling scores following a 3-week interval.

Jane was a sweet child, with an I.Q. of 96, who quickly related to the interviewer. She went on to describe her resentful feelings toward her older sister.

The parents were reassured about their daughter's detached attitude, and the management of the sibling rivalry was outlined. Jane was placed on a star chart (she received a star for each day she had not soiled) and returned the following week to report happily that she had been free of symptoms.

There was no exacerbation in the 4½ month period in which she was followed.

CASE 4.—Caroline M. was a 6-year-old girl brought to the clinic by her mother because of 3 recent episodes of fecal soiling. The child was also hyperactive and enuretic.

The first episode occurred directly following a reprimand by a teacher in an overcrowded classroom. When Caroline returned home from school, she was punished with a whipping. Within the next 3 weeks there were 2 further episodes of soiling, each following a correction given by the mother.

Caroline was adopted at 3 years of age. Little is known of her early history except that she had been placed in numerous foster homes. At the time of the adoption the mother reported that Caroline was soiling, but she went on to explain that she had things "whipped into shape" within one week.

Mrs. M. was a perfectionist who required her husband to smoke in the bathroom so as not to "smell up the house." She was an affectionate mother but had qualms as to whether Caroline might not be "born bad." The father was an easygoing sergeant in the Army. There was a younger adopted brother with whom Caroline got along well.

Caroline was a hyperactive little girl with an I.Q. of 114. She tried hard to please when demands were made of her. She quickly developed a warm relation in therapy and told of her fears and her dreams of being taken away from home.

Following her third visit, there were no further episodes of enuresis or soiling. Her schoolteacher was acquainted with the child and became less concerned with Caroline's hyperactivity in the classroom.

COMMON FEATURES

We have arbitrarily placed children with a history of fecal soiling of over 6 months' duration in the chronic group and children with symptoms of less than 6 months in the acute group.

Ten of the 12 reported cases were in the chronic group, and it was noted that many of these children had features in their histories which were similar. A typical case might be reported as follows: The mother complained that her child had fecal soiling dating back to the training period. In each of three children there was an interval following the completion of training in which they were symptom free. In the 7 remaining cases we were unable to obtain a reliable history to clarify this point.

The mother usually started toilet training at an early age, 6 months or before. There was often evidence of severe discipline in toilet training. Examples of being placed on the pot for long periods of time or of adhering to some schedule were frequent. The child rebelled against these coercive methods, struggling and crying when placed on the toilet. His feces were frequently deposited anywhere but in the receptacle. The child then began to withhold his bowel movements. Periods of withholding lengthened into constipation, alternating with fluid leakage. The mother invoked the assistance of relatives, neighbors, and

doctors, often to no avail. As the bowel became more distended with the accumulation of feces, there occurred the occasional passing of a hard voluminous stool. In five cases impaction occurred on two or more occasions. This event frequently precipitated a hospital admission, where routines ranging from anal sphincter exercises to daily enemas were ordered. Medication to lubricate the bowels, to increase the bulk, and to stimulate peristalsis was prescribed with varying degrees of success. The child, outwardly, appeared indifferent to it all, while the parents became more desperate with each succeeding therapeutic failure.

The family developed elaborate routines in an attempt to encapsulate the problem and, in effect, to deny its existence. The child was the focus of attention and thus became more compulsive in the increasingly rigid defenses of his family.

Eventually, the child arrived at school where he was confronted with a difficult situation. The teacher was perplexed and his schoolmates reacted in a variety of ways, from sheer disgust to relative indifference.

Referral to a children's psychiatric clinic occurred as a last resort and only after a history of many years' duration.

There were two children in the chronic group who had symptoms of staining rather than the frank release of bowel contents into the underclothes. In addition these two children had symptoms only in certain situations. For example, one child soiled on her way home from school, the other child soiled himself only in the home. Both children were free of symptoms at various times. One went into remission while receiving laxatives from the family doctor. The other child was free of symptoms while away on a vacation. Neither child had a history of impaction. Both children responded quickly to therapy.

Two children were in the acute group (symptoms of 6 months or less). A traumatic event was felt to be a precipitating factor in both cases. These children were completely trained after a short period of therapy.

MANAGEMENT

The majority of our cases, at some time in their history, were investigated to rule out the possibility of organic disease. In those cases where this investigation was not done, a complete physical examination was made and a history was taken. If this was diagnostic of psychogenic megacolon, no further studies were ordered.

We then took a complete psychiatric history from the parents in an attempt to understand the child and his interaction with his environment. Particular attention was paid to the training attitudes and the behavior of the parents. In addition any traumatic experience affecting the child was fully explored.

In the ensuing clinic visits two doctors worked in close conjunction, one interviewing the parents and one interviewing the child. The patient was encouraged to act out his feelings in play therapy, clay modeling, and finger painting. In the older children discussion supplemented the above procedures.

The parents were handled with sympathy and with firm support. The first step was to alleviate the intense concern which had developed over the

years in relation to the problem. One or both parents were frequently noted to have obsessive traits which made them difficult to manage by nondirective psychotherapy. From experience, we learned to be firm and *explicit* in our advice. As therapy progressed, every improvement was plainly emphasized. Many parents had the conviction that good could be done only by physical methods and medication. At times it was necessary to use this approach to gain their confidence, then subsequently to enlarge upon the emotional aspects of the case.

When the child's symptoms went into remission and the treatment was terminated too early, relapse occurred. The mothers needed prolonged support. The intervals between visits were gradually lengthened, with the understanding that should any emergency arise, the clinic would be at their disposal.

TABLE I. RESULTS

AGE (YEARS)	SEX	APPROXIMATE DURATION OF SYMPTOMS	RESULTS FROM THERAPY
13	M	9½ years	Improved
10	M	8 years	Improved
10	M	3 years	Cured
10	M	4 years	Cured
9	F	7 years	Cured
9	M	5 months	Cured
9	M	7 years	Cured
8	M	5½ years	No change*
7	F	3 years	No change
7	M	3 weeks	Cured
6	M	3½ years	Improved
5	M	2½ years	Cured

*Improved during stay at Happy Hill Convalescent Hospital.

DISCUSSION

In 2 of the 12 children encopresis was the sole complaint. Associated symptoms in the other 10 children were: enuresis 6; resistant attitudes (reported as angry, chip-on-his-shoulder, doesn't mind, difficult to handle, stubborn) 5; immature speech 4; hyperactivity 3; temper tantrums 2; withdrawn 2. Other symptoms were school phobia, feeding problems, transvestism, and fire setting.

At the clinic, the children were well mannered, cooperative, and sensitive to others' feelings. In play therapy they often demonstrated overt hostility directed toward the "mother" doll. For example, 3 children would repeatedly take a "mother" doll and push its face into the fingerpaints. Four children were immature and overdependent upon their mothers. Two other children were sullen and withdrawn. In nearly all children compulsive characteristics were noted.

The encopretic child, by nature of his symptoms, invited considerable reaction from his environment. Mothers usually handled the problem with persistent nagging interspersed with periods of emotional outbursts, thus keeping the child in a chronic state of agitation.

The finding of obsessional traits in the parents has been noted. We hasten to add that our group of 12 families included 40 siblings, none of whom had any history of encopresis. One concluded that other factors were acting. These obsessive traits were seen more often in the mother. The father usually was an easygoing nonchalant individual. The mother was apt to be unhappy about her lot in life. She would go on at length discussing family responsibilities that fell on her shoulders. Eight out of 12 mothers reported working outside the home for a significant length of time, ostensibly to improve living conditions. Six women had major complaints of being unsatisfied with their husbands in some respect. For example, one child told

his mother of his intentions to be a minister like his father. The mother reported that she "soon poisoned his mind of the pulpit." Another wife reported her husband was unable to handle strong emotions so she looked for an outlet in other men. One wife worried about feminine traits in her husband and was certain the boy would grow up like his father. This tendency on the part of the mother to identify the patient with some unfavorable aspect in his father's behavior was seen on more than one occasion. Four mothers were overprotective and fostered ways of keeping the child in a dependent relationship. For example, one mother dressed her boy until he was 8 years old; another mother slept in the same bed with her son until he was 9.

In most cases a simple cause and effect relationship could not be demonstrated to explain the development of the symptoms. In some cases there was a coming together of events, highlighted by some traumatic incident, at which time encopresis developed. For example, one girl until 4 years of age was treated as the baby of the family. At that time, she developed a severe febrile illness and became dehydrated. She was treated at home for two weeks, with hourly enemas administered by her parents. Shortly following this she developed symptoms of fecal soiling. Another child while in the process of toilet training had an older sister develop poliomyelitis. The family attention was directed to the sister and the child was finally toilet trained by 3 years of age. He later became encopretic during a period of intense sibling rivalry. Another child was managed successively by three different people during his toilet training. He developed encopresis upon entering school.

There seemed to be a coming together of events, superimposed on a background of perfectionism, from which the symptom arose and by its very nature was focused upon and reinforced by parental reaction. The encopretic child, in turn, had a means of causing the offending parent much labor and worry. So a vicious cycle is completed.

In order to understand and remove this symptom-complex, there appeared to be no substitute other than the intimate knowledge of each child and his peculiar relation to his environment.

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THE OCCURRENCE OF A POSITIVE COOMBS TEST IN A CASE OF GALACTOSEMIA

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GALACTOSEMIA, a relatively rare metabolic disorder, is now a well-established clinical entity, and approximately 50 cases have been reported. Early detection is necessary so that the severe consequences of the disease may be avoided. This particular case is being reported because of the unusual finding of a positive Coombs test in the laboratory investigation.

CASE REPORT

This apparently normal 3.4 kilogram boy was born spontaneously at home attended by a physician after an uncomplicated pregnancy. The mother and father as well as 3 siblings of ages 3, 6, and 9 years, respectively, were normal, and there was no history of serious illnesses. The mother had had no abortions or stillbirths.

The infant was breast fed and had routine newborn infant care. Late on the second day of life the mother noticed mild jaundice which deepened over the next 5 days and then regressed but never completely disappeared. He ate well without vomiting but had loose stools which were occasionally green.

At 3½ weeks of age he weighed 3.2 kilograms and was taken to another physician because of jaundice and failure to gain weight. The examination revealed a lethargic infant with jaundice and hepatomegaly. Laboratory data revealed a white cell blood count of 9,300 per cubic millimeter, with 40 per cent neutrophils, 5 per cent stabs, and 55 per cent lymphocytes; an absence of circulating nucleated red cells; a packed cell volume of 40 mm.; a positive direct Coombs test; and the mother's and baby's bloods were type A, Rh positive. The baby's urine contained a trace of sugar, 1+ protein, and was positive for bile; the stools were also positive for bile.

When the baby was referred to the University Hospital at 4 weeks of age, he was pale, malnourished, jaundiced, and lethargic. The abdomen was distended and the abdominal veins prominent. The liver was enlarged 4 cm. below the right costal margin and extended across the midline into the left upper quadrant. The examination was otherwise not remarkable.

Initial laboratory studies here were as follows: packed cell volume, 40 mm.; white cell blood count, 19,300 per cubic millimeter, with 18 per cent neutrophils, 57 per cent lymphocytes, and 25 per cent stabs; reticulocyte count, 0.8 per cent; direct serum bilirubin, 7.2 mg. per cent; indirect serum bilirubin, 7.2 mg. per cent; Kahn, negative; and direct Coombs test, positive. The urine was negative for protein but contained 4+ sugar which failed to initiate a color change with Tes-Tape or Uristix, tentatively ruling out glucose. No cytomegalic inclusion bodies were found in the urine.

Qualitative urine sugar determinations were done by the Nelson modification of the Somogyi method for

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exclusion of non-sugar-reducing substances.[1] A urine specimen taken while the baby was on a milk diet contained 700 mg. per cent of sugar when the 24-hour urine volume averaged 300 ml.

A diagnosis of galactosemia was suspected and Mullsoy feedings were started. The urine sugar dropped to 78 mg. per cent in 12 hours, 30 mg. per cent in 24 hours, and was not detectable in 36 hours. One week later milk was again given for 24 hours and the urine sugar rose to 1,440 mg. per cent by the end of this period.

Fig. 1.—The infant is shown here at 4 weeks of age just after lactose was removed from the diet. The liver edge is outlined.

It dropped to 232 mg. per cent in 24 hours after Mullsoy was reinstituted and was not detectable in 36 hours. After 2 weeks of Mullsoy feedings the jaundice disappeared, the liver decreased markedly in size, and the infant started to gain weight. Fig. 1 shows the baby just after lactose was removed from the diet.

Descending paper chromatography after the method of Natelson[2] demonstrated that the urine sugar migrated exactly the same distance as control galactose. The strips are shown in Fig. 2. The urine used for the chromatographic studies was collected while the baby was on milk feedings. The filter paper strips were scanned with a Spinco Analytrol Scanner. The tracings are shown in Fig. 3. This identification of the urine sugar obviated the use of the galactose tolerance test with its attendant dangers.

The most interesting aspect of this case was the positive Coombs test which prompted the referral of the baby here with a diagnosis of inspissated bile syndrome subsequent to hemolytic disease. An attempt was made immediately to demonstrate an isoantibody in the mother's serum. The baby and mother, however, had identical ABO blood groups and identical Rh genotypes. Both were type A, Rh positive and carried Rh factors D, C, c, and e. If the mother was forming an isoantibody, the antigen carried by the infant obviously was uncommon. A test cell panel supplied by the Knickerbocker Laboratories was set up by the University blood bank. This panel consisted of 22 different blood group antigens and no isoantibody against any of these could be detected in the mother's serum. Samples of maternal and infant blood were then sent to the Ortho Pharmaceutical Laboratory for further investigation and no antibodies were detected.

By the use of the indirect Coombs test, the factor or substance responsible for the agglutination was shown to be associated with the baby's cells and serum. The results are recorded in Table I. The mother's serum was free of agglutinating activity. The strongest agglutination occurred when the infant's serum and either the

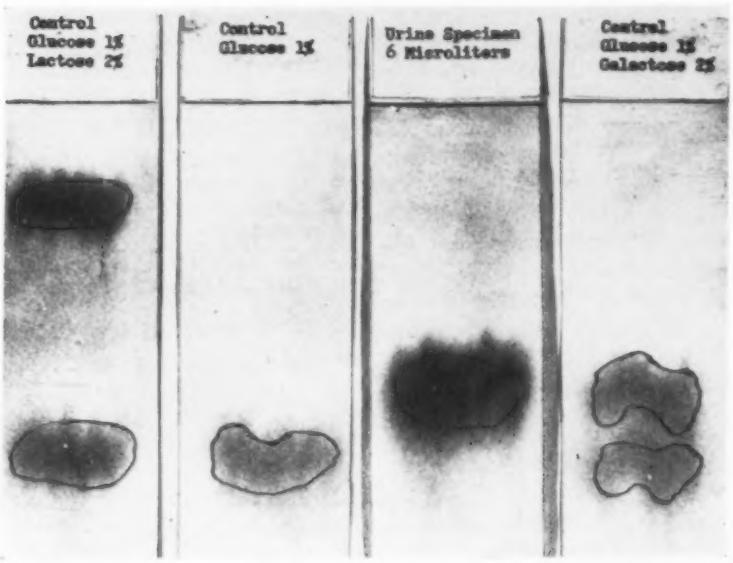

Fig. 2.—Paper chromatography showing migration of urine galactose and controls.

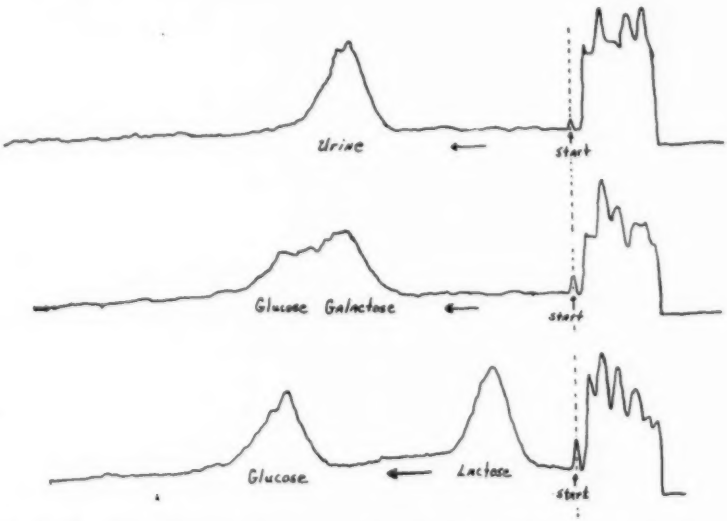

Fig. 3.—Photoelectric tracings of chromatographic patterns in Fig. 2 are shown here. Tracings were made with a Spinco Analytrol Scanner.

mother's cells or control type A, Rh positive cells were used. It is interesting that the results could not be repeated when the infant's cells were trypsinized and incubated with AB plasma, albumin, dextran, and galactose solution. Trypsinization usually enhances agglutination in Coombs serum. The direct Coombs test was positive on 2 occasions, once at the outlying dispensary and once on admission here, but it could not be demonstrated again. The infant was seen 3 weeks after the original blood samples were drawn, and the tests in Table I were repeated but were all negative.

ing this enzyme for metabolism of galactose are as follows:

1. galactose + ATP $\xrightarrow{\text{galactokinase}}$ galactose-1-phosphate + ADP
2. galactose-1-phosphate + UDPG $\xrightarrow[\text{galactose-1-phosphate uridyl transferase}]{}$ glucose-1-phosphate + UDPGal
3. UDPGal $\xrightarrow[\text{UDPGal-4-epimerase (galactowaldenase) DPN}]{}$ UDPG

The enzyme, galactose-1-phosphate uridyl transferase, is necessary to catalyze the reaction in which galactose-1-phosphate reacts with uridine

TABLE I. SEROLOGICAL DATA

INCUBATED AT 37° C. FOR 30 MINUTES		AGGLUTINATION OF CELLS IN COOMBS SERUM
SUSPENDING MEDIUM	CELLS	
Mother's serum	Infant's cells	+
Mother's serum	Control A+ cells	0
Infant's serum	Mother's cells	+
Infant's serum	Control A+ cells	+
Control serum	Infant's cells	+
AB plasma	Infant's trypsinized cells	0
AB plasma	Mother's trypsinized cells	0
AB plasma	Control A+ trypsinized cells	0
Albumin	Infant's trypsinized cells	0
Albumin	Mother's trypsinized cells	0
Albumin	Control A+ trypsinized cells	0
Dextran	Infant's trypsinized cells	0
Galactose solution (2 per cent)	Infant's trypsinized cells	0

DISCUSSION

Galactosemia was first described in 1908 by von Reuss[3]; Goppert[4] wrote of the familial nature of the disease in 1917, but the first paper to appear in the American literature was by Mason and Turner in 1935.[5]

The basic defect in this disorder is biochemical. Recent work by Isselbacher and co-workers[6-8] has shown that a single enzyme deficit accounts for the abnormal galactose metabolism. The proposed chemical reactions utilizdiphosphoglucose to form uridine diphosphogalactose (reaction 2). The absence of this enzyme results in an accumulation of galactose-1-phosphate in red cells and many fixed tissue cells, especially in the liver. A procedure for detection of galactose-1-phosphate in erythrocytes of cord blood is now being investigated.[9]

Pathologic changes in the disease have been attributed to low blood glucose levels by Mason and Turner,[5] but Mellinkoff and associates[10] questioned

this hypothesis and were the first to suggest that elevated serum and tissue galactose were the toxic factor. It is now generally accepted that accumulation of unmetabolized galactose-1-phosphate results in cellular damage.[11-13] Results of this damage are evident from observations on metabolic changes in erythrocytes and microscopic changes in renal and hepatic cells, the lens of the eye, and the central nervous system.

Three clinical variations of the disease have been described.[14] In severe cases signs and symptoms appear within the first 2 weeks of life and consist of vomiting, loss of weight, lethargy, failure to thrive, loose stools, rapid enlargement of the liver, ascites, proteinuria, galactosuria, amino-aciduria, and cataracts in a few instances. The case under discussion falls into this group.

A second group includes infants who do well for a few weeks or months and are then brought to the physician because of poor appetite, lethargy, and physical retardation. They have hepatomegaly and a high percentage have cataracts. These children are not acutely ill, and their mentality is usually fair.

There is a third group consisting of older infants and children who eat poorly from birth and never especially care for milk. There is often a history of early weaning. This type of case is usually picked up while a sibling is ill with the disease.

The clinical signs and symptoms of patients in these categories have been reviewed in several excellent papers.[8, 12-15] This case adds nothing new to the typical picture.

No reference to a positive Coombs test as a part of this disease could be found in the literature reviewed. Bain and associates[15] report negative tests in their 8 cases, and Komrower and his colleagues[12] also report negative tests in their series. In the majority of case reports reviewed, there was no mention of the Coombs test.

The presence of an autoantibody in the infant's circulation was considered but seemed unlikely at such an early age. Hemolysis is the usual response to autoantibodies, but the high stable packed cell volume, low reticulocyte count, absence of nucleated red cells and microspherocytes, and high direct bilirubin level are against destruction of red blood cells in this case.

Antibodies which are attached or have the ability to attach to the erythrocyte membrane account for the agglutination in the classic Coombs test. However, erythrocytes may occasionally clump in Coombs serum without the presence of an antibody. Muirhead and Graves[16] report that phenylhydrazine given intravenously to dogs results in a positive Coombs test using the animal's washed erythrocytes suspended in saline and have shown that this is a nonimmune response. They have also demonstrated that certain lipid solvents in vitro cause clumping of canine erythrocytes in Coombs serum. These solvents include acetone, toluene, benzene, xylene, dioxane, ether, ethyl alcohol, petroleum ether, and chloroform. These workers have postulated that phenylhydrazine in vivo and lipid solvents in vitro injure the red cell membrane, altering it in one of the following ways: normal intracellular proteins may be exposed through the

damaged membrane; intracellular proteins may be denatured, thus altering the cell; or plasma proteins may be adsorbed onto the injured cell membranes. One of these alterations may account for the agglutination in Coombs serum. They have shown that stronger agglutination occurs when canine whole blood is used rather than washed erythrocytes, an indication that adsorbed plasma proteins may be the mechanism of agglutination.

Jandl and Simmons[17] report that certain metallic cations such as Cr^{+++}, Fe^{+++}, Be^{++}, Th^{++++}, Al^{+++}, and Cu^{++} have the ability to attach protein to the red cell membrane and cause agglutination in Coombs serum which is indistinguishable from agglutination by complete antibodies. Sutherland and Eisentraut[18] report a positive Coombs test using erythrocytes from patients with lead poisoning. They postulate that damage to the cell membrane allows intracellular globulin groups to project to the surface or that globulins are adsorbed from the plasma onto the cells.

A number of other substances cause either direct agglutination of erythrocytes or a positive Coombs test. Jandl and Castle[19] have shown that large anisomeric molecules such as dextran, gelatin, polyvinylpyrrolidone, human ovarian cyst pseudomucin, carboxymethylcellulose, gastric mucin, gum arabic (6 beta-glucuronasylgalactose), and sera of patients with multiple myeloma often cause a positive Coombs test.

Several investigators have reported metabolic abnormalities of erythrocytes from galactosemic patients.[6, 7, 11, 12] Schwarz and Komrower state that red cells from a galactosemic infant or child are damaged by anoxia which results from accumulation of galactose-1-phosphate within the cell and that these cells do not respire in a galactose medium. The oxygen uptake is extremely low in any media, and resulting anoxic changes perhaps result in unusual agglutinating tendencies.

SUMMARY

A case of congenital galactosemia has been presented with a discussion of diagnosis by using filter paper chromatography. The method entails very little danger to the infant.

The biochemical abnormalities in this disease, now well substantiated, depend upon a single enzyme defect. These changes are due to the absence of a transferase; this allows accumulation of galactose-1-phosphate in blood and within fixed tissue cells.

The interesting finding of a positive Coombs test associated with galactosemia has been presented, and nonimmune mechanisms of erythrocyte agglutination have been discussed.

I wish to thank Dr. Abe Siegel and Dr. S. D. Palmer of the Clinical Laboratory of the University Hospital and Miss Katheryn Melonas of the University Hospital Blood Bank for their assistance in the laboratory investigation of this case.

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HEREDITARY ENAMEL DYSPLASIA

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HEREDITARY enamel dysplasia is a rare developmental anomaly of the teeth resulting from malfunction of the enamel organ. The disturbance is of ectodermal origin, the mesodermal components of the teeth being unaffected except secondarily, due to rapid loss of the affected enamel. This anomaly has been referred to as brown opalescent teeth,[1] brown discoloration of enamel,[2] hereditary brown teeth,[3] amelogenesis imperfecta hereditaria,[4] and lastly as hereditary enamel dysplasia.[5] The last two terms are more scientific and more descriptive of the underlying disturbance. The term "hereditary enamel dysplasia" is preferred by the authors because of its conciseness.

The anomaly was first described in 1890 by Spokes,[3] but it was not until 1938 that Finn, on clinical and roentgenographic evidence, separated it from hereditary dentinogenesis imperfecta.[2] He reviewed 41 cases of hereditary defects of tooth color from the literature and classified 28 as opalescent dentine and only 3 as brown hypoplasia of enamel. The remaining 10 cases were not classified since they lacked adequate description. He also challenged the authenticity of some cases which were reported as complete agenesis of enamel. He considered them as cases of opalescent dentine in which enamel had been lost through attrition or friability. Weinmann, Svoboda, and Woods[4] separated hereditary enamel dysplasia into hypoplastic and hypocalcified types. In the hypoplastic variety the enamel was considered normal in quality but deficient quantitatively. The teeth were described as hard, smooth, glossy, and brownish yellow in color. The enamel, roentgenographically, was invisible due to its extreme thinness. In hypocalcification, according to these authors, the enamel matrix was considered to be normal in amount but defective in calcification. The teeth were soft, rough, dull, and dark brown in color. The enamel was indistinguishable from the dentine on roentgenographic examination. Subsequent to the publication of this article, only a few cases have been reported in the literature.[6-15]

The etiology of the disease is not clearly understood. No local or systemic factors can be held responsible for this developmental disturbance. It is considered to be hereditary and is possibly transmitted as a simple dominant mendelian character without

From the Divisions of Oral Pathology, and Oral Diagnosis, School of Dentistry, University of Minnesota, and the Department of Oral Diagnosis, School of Dentistry, Indiana University.

apparent sex-linkage. However, there are cases on record[11, 13, 15] in which no hereditary background could be traced. tary background. These cases have been referred to as idiopathic and are not included in this study.

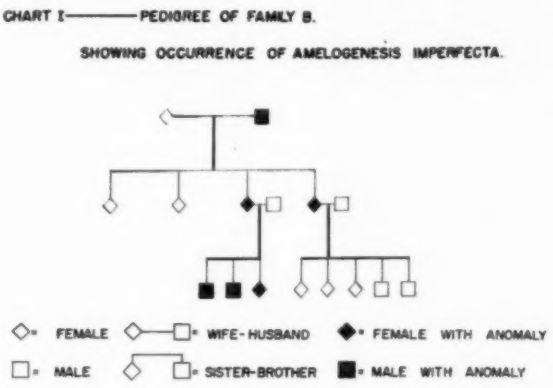

Fig. 1.

MATERIAL FOR THE STUDY

The material for this publication has been collected from the files of the University of Minnesota, School of Dentistry, and based on the genealogic histories of 5 families. In addition, there were 3 other families in which 2 sisters, a sister and 2 brothers, and an only child, respectively, had teeth with clinical and roentgenographic features similar to enamel dysplasia but without any determined hereditary background. These cases have been referred to as idiopathic and are not included in this study.

CASE HISTORY

Family B.—The pedigree of family B is illustrated by chart I, Fig. 1. A 43-year-old white woman was first seen at the dental school in 1949, at which time she was completely edentulous. She stated that her teeth were extracted when she was 25 years of age. She described them as brown, soft, and friable. Her present visit was intended for procurement of new dentures. On routine roentgenographic examination, an unerupted maxillary third molar tooth was noticed. The

Fig. 2.—*Family B* (daughter, 12 years of age). Photograph of teeth showing loss of enamel from the surfaces. Note the remnants of enamel in the gingival portion of the crowns.

Fig. 3.—*Family B* (same as Fig. 2). Roentgenograms showing deformed and/or resorbed crowns and lack of eruption of teeth.

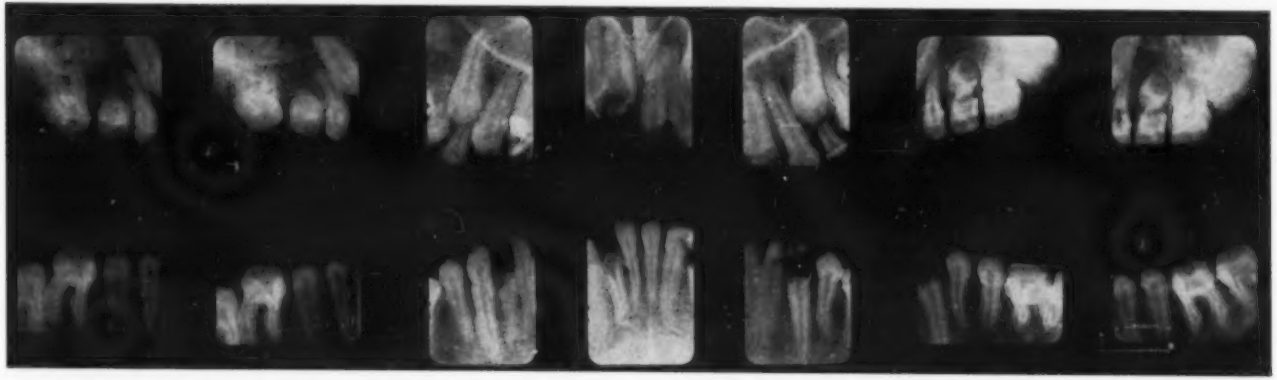

Fig. 4.—*Family B* (older son, 13 years of age). Roentgenograms showing typical features of the anomaly. Note absence of tooth germ of 5 |

appearance of the enamel was not unlike that of hereditary enamel dysplasia.

Her daughter was first seen at the School of Dentistry in 1949, at which time she was 8 years old. Roentgenographic examination at that time revealed involvement of both her deciduous and her permanent dentitions. Clinically, her teeth were described as light yellow in color and covered irregularly with a thin layer of soft, friable, dull, and lusterless enamel. Fig. 2 is the photograph of her teeth which was taken on Jan. 30, 1953.

phorus analysis was performed by the method of Fiske and Subbarow[17] and calcium analysis by that of Clark and Collip.[18] The data indicated that the organic content of enamel in amelogenesis imperfecta was 8.66 per cent, compared with a normal value of 4.48 per cent.

The clinical appearance of the teeth of her (mother, of family B) eldest son was similar to that of his sister. Fig. 4 shows the roentgenograms of his teeth which were taken on Nov. 30, 1953, at the age of 13 years. Again, involvement of both dentitions was

Fig. 5.—*Family B* (younger son, 4 years of age). Photograph showing pigmented defective enamel with its partial absence from some teeth.

The teeth were deep yellow in color and were completely devoid of enamel except for the cervical third of the crown where it formed a collar around the tooth. Roentgenograms taken on Dec. 1, 1953, are shown in Fig. 3. Prolonged retention of C A | C was associated with delayed eruption of 3 1 | 3. Defective crown formation and/or resorption was evident in some teeth. The crown of the upper left canine appeared to be completely resorbed. The dental root canals were clearly apparent. In 1955, all of her teeth were extracted and complete upper and lower dentures were made. Chemical separation of enamel and dentine was performed by the flotation method described by Manly and Hodge.[16] Samples to be tested were subjected to dry heat at 500° to 700° C. to remove all organic matter. Phos-

apparent. Similarly, the deformity of the crowns of some teeth was evident. Another noticeable feature was the absence of the dental organ of the right upper second bicuspid tooth and the apparent delay in development of the left upper second bicuspid.

Fig. 5 shows the teeth of her youngest son who was first seen in 1955 at the age of 4 years. His teeth were of yellowish-brown color, with pitting of the maxillary central incisors. They were partially covered with enamel which was chalky and lusterless. Roentgenograms showed the absence of developing crowns of 5 4 | 4 5 teeth.

Family D.—The pedigree of family D is illustrated by chart II, Fig. 6. The presenting patient was 16 years old when first seen in 1954. Fig. 7 is the photograph of her teeth taken at

that time. The crowns of her maxillary central incisors were completely destroyed and the remaining portions were devoid of enamel. The roentgenograms were characteristic of hereditary enamel dysplasia. Her younger sister was 15 years old, and the clinical appearance of her teeth was similar to that of her sister except that the exposed dentine of her upper anterior teeth was deeply stained from imbibition of exogenous pigments (Fig. 8.). Furthermore, on the labial and lingual surfaces there were remnants of chalky brittle enamel. Roentgenograms were, again, typical of hereditary enamel dysplasia.

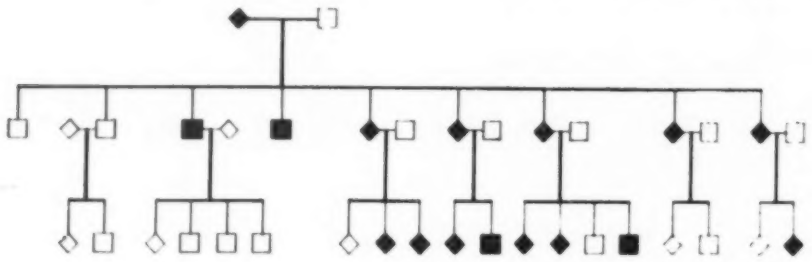

CHART II——PEDIGREE OF FAMILY D.

SHOWING OCCURRENCE OF AMELOGENESIS IMPERFECTA.

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 7.—*Family D* (older sister, 16 years of age). Photograph showing loss of crowns of maxillary central incisor teeth and absence of enamel from the surfaces of other crowns. Anterior open bite.

Fig. 8.—*Family D* (younger sister, 15 years of age). Photograph of teeth showing deep pigmentation of exposed dentine and open bite.

Family F.—The pedigree of family F is shown by chart III, Fig. 9. Two cousins, members of this family, were

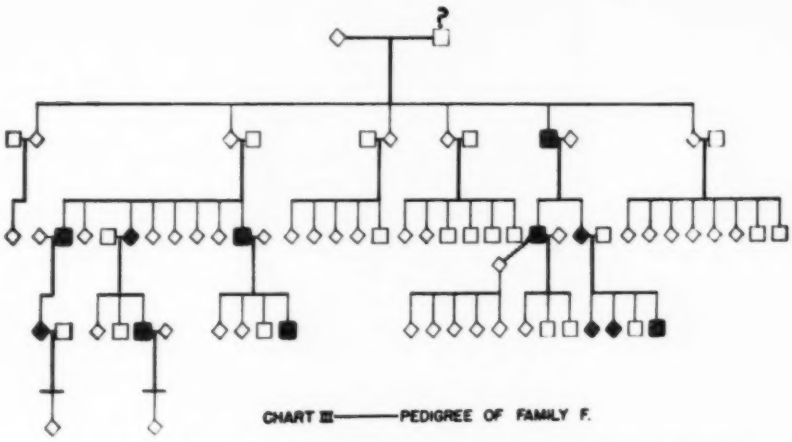

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 10.—*Family F* (older cousin, 13 years of age). Photograph showing pigmented defective enamel on the upper anterior teeth. Note partial loss of enamel from the teeth surfaces.

Fig. 11.—*Family F* (younger cousin, 5 years of age). Photograph showing relatively normal enamel covering the upper and lower central incisor teeth. Partial loss of enamel from the surfaces of cuspids and posterior teeth.

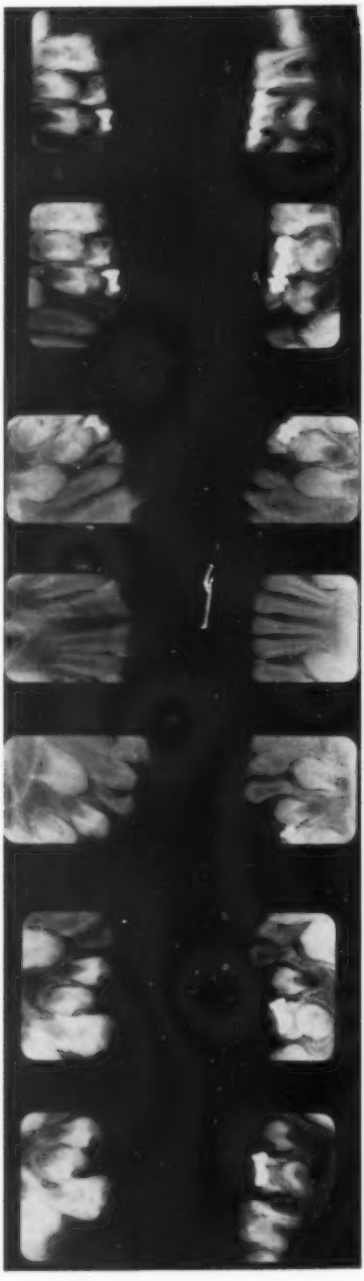

Fig. 12.—*Family F* (same as Fig. 11). Roentgenograms made when the patient was 7 years old show loss of enamel from the upper and lower central incisor teeth. Note the involvement of the 6-year molars.

seen in the dental school; the older one was 13 years old when first seen in 1950. Fig. 10 is the photograph of his teeth taken at this time. The crowns in part had retained their enamel, which was chalky and brittle and was deeply pigmented in the upper incisor teeth. The roentgenograms showed the enamel defect characteristic of the malady. The younger cousin was first seen in 1953 at the age of 5 years. His lower permanent central incisor teeth were erupted and appeared to be covered with normal enamel at this time (Fig. 11). However, the roentgenograms taken two years later showed partial loss of enamel from the coronal surfaces (Fig. 12). Interestingly enough, this patient had a twin brother who had normal teeth.

Family K.—A detailed history in this family is not available except for brief information in one dental record. A 14-year-old white girl was seen at the University Hospital for mastoiditis in 1948. She was referred to the School of Dentistry for a routine examination. Her teeth were described as yellowish brown and soft except for the lower incisors which were chalky white and lusterless. The roentgenograms were indicative of the disease. The lower central incisors were normal in shape and were covered with a thin layer of enamel which could hardly be differentiated from the underlying dentine. Her mother had stated that 4 of her 6 children were afflicted with this anomaly. Her only son had his teeth extracted at the age of 15 years. The disorder was present in her husband and his family. Her husband had a sister with this defect and she, in turn, had several children suffering from the disturbance.

DISCUSSION

It would appear from the genealogic charts that siblings manifest the condition only when one of the parents has the defect. It affects offspring of both sexes. No instances have been uncovered in which both parents had this anomaly so that the homozygous hereditary pattern is not known. The anomaly involves only the enamel which usually is brittle and friable and is rapidly lost from the tooth surfaces exposing the dentine which is structurally normal. The exposed dentine is sensitive to external stimuli and its peripheral layers, especially on the occlusal surfaces, often become sclerotic. Only a small amount of secondary dentine was formed in the teeth of the young people examined, and the root canals were of the usual size for the respective ages.

The literature concerning this developmental defect is scant and difficult to evaluate, particularly because of two factors: (1) Some authentic cases of enamel dysplasia lack hereditary background in spite of the fact that their clinical and roentgenographic features are similar. Until a sound explanation is available, it may be advisable to classify these cases as idiopathic. (2) Further classification of hereditary enamel dysplasia into hypoplastic and hypocalcified varieties[4] has added to the complexities of the problem. It is possible that the hypoplastic form is relatively uncommon and, therefore, not encountered in this series. Nevertheless, the clinical and roentgenographic features of the two types overlap and, therefore, their distinction from one another becomes exceedingly difficult, if not impossible. It would seem that this distinction may be more of academic interest than of clinical significance. It is the degree of disturbance of amelogenesis which is critical.

In the milder forms, the affected teeth have been preserved by placing

temporary and later permanent crowns. In extremely severe cases, some of the patients exhibited marked disturbances in occlusion, especially open bite, which may have been due partly to a secondary disturbance in the development of the jaws. In such cases, extraction of teeth and their replacement by dentures has enhanced esthetics as well as the mechanical efficiency of the masticatory apparatus.

SUMMARY AND CONCLUSIONS

A brief review of the literature and a detailed clinical and roentgenologic examination of the teeth in 10 members from 5 families with a known pedigree has led the authors to form the following conclusions:

1. Hereditary enamel dysplasia is an hereditary disturbance which appears to be transmitted as a simple dominant mendelian character without apparent sex-linkage. Similar cases which lacked an hereditary background were not included. The authors have preferred to consider them to be idiopathic in origin.

2. This anomaly is primarily an ectodermal disturbance of the tooth germ, the mesodermal components being normal. Secondarily, the exposed dentine may become sclerotic.

3. No case of complete enamel agenesis was found in the present series. However, in some cases there was a small quantity of enamel which broke off soon after eruption of the teeth. There was a gradation in the degree of disturbance. The enamel in newly erupted teeth was white, dull, and chalky but soon became pigmented due to imbibition of exogenous pigments.

4. Both dentitions were affected in all patients of this series.

5. Other abnormalities, namely, tooth resorption, missing teeth, localized delayed eruption, and anterior open bite were noted in some cases but were not present consistently.

6. From the point of view of treatment, the degree of involvement is of importance. In mild cases, crowning the teeth has been successful, while in severe cases, especially those with severe malocclusion, extraction of teeth and construction of dentures to improve esthetics and function have been indicated.

We are grateful to Dr. Leon Singer, Associate Professor, Department of Physiological Chemistry, for his help in performing the chemical analyses of teeth.

We also wish to express our gratitude to Mrs. Barbara Chaudhry for making genealogic charts for this study.

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"To such a degree is this terrible disease [diphtheria] contagious, a few in the profession refusing to acknowledge it, and the majority of the people persistently refusing to isolate their children, it appears to me that the only method by which we can prevent the spread of diphtheria is by the enactment of laws compelling the people to assume some responsibility in regard to contagious diseases."

Chas. Warrington Earle, M.D., on Diphtheria, from Transactions of the Ninth International Medical Congress, 1887.

HEREDITARY DENTINOGENESIS IMPERFECTA

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HEREDITARY dentinogenesis imperfecta, as the name implies, is a developmental disturbance in the formation of dentine. The anomaly, according to Finn,[1] was first reported in 1882 by Barrett. It has been described in successive generations in a number of families in Europe as well as in this country. The condition has been referred to as hereditary opalescent dentine, dentinogenesis imperfecta hereditaria, and odontogenesis imperfecta.[2] The most commonly used term is hereditary opalescent dentine, but a more appropriate and descriptive one is hereditary dentinogenesis imperfecta.

The anomaly is not related to any dietary or endocrine imbalance or infectious disease. Hodge and co-workers[3] during their clinical studies found that the basal metabolic rate, differential blood count, blood chemistry (including calcium, phosphorus, blood sugar, and total cholesterol), and urinalysis were all within normal limits. Serologic tests for syphilis also were negative. The only consistent abnormal finding was elevated plasma phosphatase. Other members of the family without this condition also had higher than normal values. Similarly, chemical and bacteriologic studies of the saliva of patients with opalescent dentine have been found to be within normal range.[4]

The hereditary factor responsible for this anomaly is probably a nonsex-linked dominant factor. Rushton[5] cited reported cases in which the maternal uncle, a nephew and a niece, but not the mother, were visibly affected. To our knowledge, no record of a marriage between individuals with hereditary dentinogenesis imperfecta has been published so that the inheritance pattern of the homozygous condition is not known.

Clinically, the teeth may be of normal size and shape, or the crowns may be normal and the roots smaller in size, or there may be an over-all decrease in the size of both the crown and the root. The crowns are prone to rapid attrition. It is not unusual for them to be worn down to gum level shortly after eruption. The early loss of enamel has been attributed either to "soft enamel" or to lack of scalloping which is normally present at the dentino-enamel junction. Full complements of deciduous and permanent dentitions are commonly involved. However, cases are on record in which the authors have claimed involvement of only one dentition or a part of the tooth.[5, 6] The teeth with

From the Divisions of Oral Pathology and Oral Diagnosis, School of Dentistry, University of Minnesota, and the Division of Oral Diagnosis, School of Dentistry, Indiana University.

this condition are translucent and their color varies from blue gray to brown or blue brown. When covered with normal enamel, the teeth are usually smooth and shiny but occasionally their surfaces may have pits and fissures due to enamel hypoplasia. Unlike amelogenesis imperfecta, the loss of enamel and dentine, due to attrition, is normal. Owing to the presence of self-cleansing surfaces from rapid attrition, a low incidence of caries has been described in this condition.[1-3] This may not hold true in all patients.[7]

finding.[1, 3, 8] Similarly, fracture of roots is commonly noticed.[1, 8]

Chemically, Hodge and associates[9] found the dentine to have a higher water content, a higher organic content, and a lower inorganic content than normal dentine. The calcium and phosphorus percentages were within normal range; however, the calcium–phosphorus ratio was slightly higher than normal. Physical studies showed the density of the anomalous dentine to be less than normal, as would be expected from its higher water content. In microhardness tests,

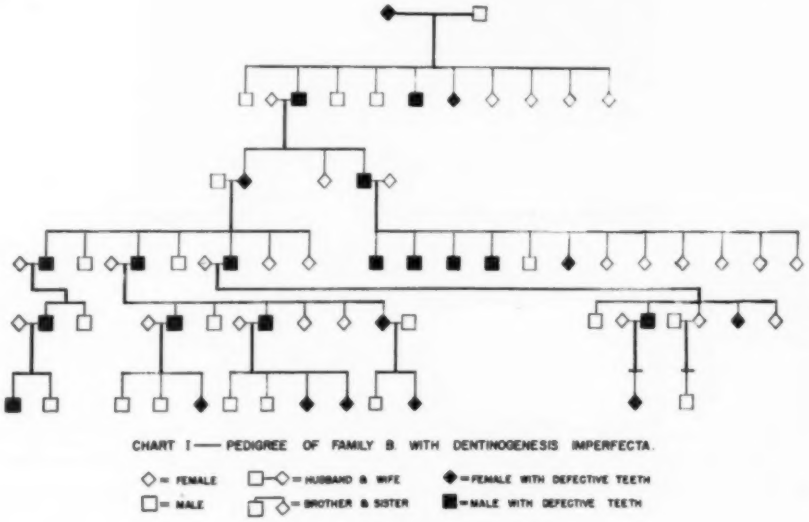
CHART I — PEDIGREE OF FAMILY B WITH DENTINOGENESIS IMPERFECTA.
= FEMALE
= MALE
= HUSBAND & WIFE
= BROTHER & SISTER
= FEMALE WITH DEFECTIVE TEETH
= MALE WITH DEFECTIVE TEETH

Fig. 1.

Roentgenographically, the roots may be of normal size and shape but more often they are short and the necks of the teeth appear to be constricted and the root ends are spiked. There is an early partial obliteration of the pulp chambers and root canals. There also may be thickening of the periodontal membrane. Several authors have claimed that periapical pathosis in teeth with this condition is a common

the defective dentine was found to have a value of only 65 compared to normal dentine which has a value of 125.[9]

MATERIAL FOR THE STUDY

The material for this study was collected from the files of the School of Dentistry, University of Minnesota. A detailed genealogic history is available from three families.

CASE HISTORY

Family B.—The pedigree of this family is illustrated by chart I, Fig. 1. A 17-year-old white girl was first seen in the oral diagnosis clinic in December 1952. Her teeth were described as smooth and translucent with a grayish-blue hue. There was marked attrition, especially of the anterior teeth (Fig. 2). She stated that her deciduous dentition was of the same color. She had enjoyed excellent health without any history of hospitalization. Roentgenographic examination revealed an over-all reduction in the size of her teeth. The roots were short with constricted necks. The pulp chambers and root canals were partially or completely obliterated, radiographically (Fig. 3). In contrast to the findings of other investigators,[1-3] there were several carious teeth present without apparent periapical pathosis, except in connection with the left upper lateral incisor tooth. The anomaly could be traced back six generations with certainty. Of 60 members, 26 were affected by this disorder. Of these, 11 were females and 15 were males. It is quite evident from the family tree that the disease manifested itself in the sibling only whenever one of the parents was affected. Thus, the condition appeared to be dominant and heterozygous in character without apparent sex-linkage.

The patient had her unerupted impacted left lower third molar tooth extracted. The tooth was split into two parts and was immediately immersed in formalin fixative. One half of the tooth was used to prepare a ground section and the other half was embedded in paraffin for hematoxylin and eosin staining.

The ground section showed normal enamel both quantitatively and qualitatively. The dentino-enamel junction was straight and lacked normal scalloping (Fig. 4). The dentinal tubules were sparse, irregular in size and shape, with marked branching. Numerous interglobular spaces were indicative of poor calcification.

The decalcified sections exhibited marked reduction in the size of the pulp, which was partially obliterated by defective dentine, with no structural differentiation into primary and secondary types. The pulpal tissue was fibrotic, and odontoblasts were unidentifiable, but this may have been an artefact caused by the unusual method of preparation of the specimen.

The patient had brought her niece (brother's daughter) to the Clinic for examination of her teeth. She was only 2 years of age, and her teeth were of normal size but were translucent and of a grayish-blue color. The lower central incisors showed early attrition.

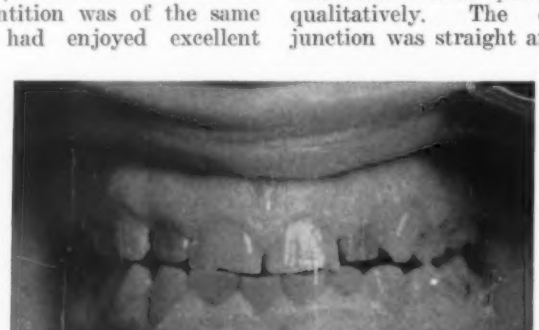

Fig. 2.—*Family B.*—Photograph showing the clinical appearance of the teeth of a 17-year-old girl. Note the color of the teeth and their marked attrition.

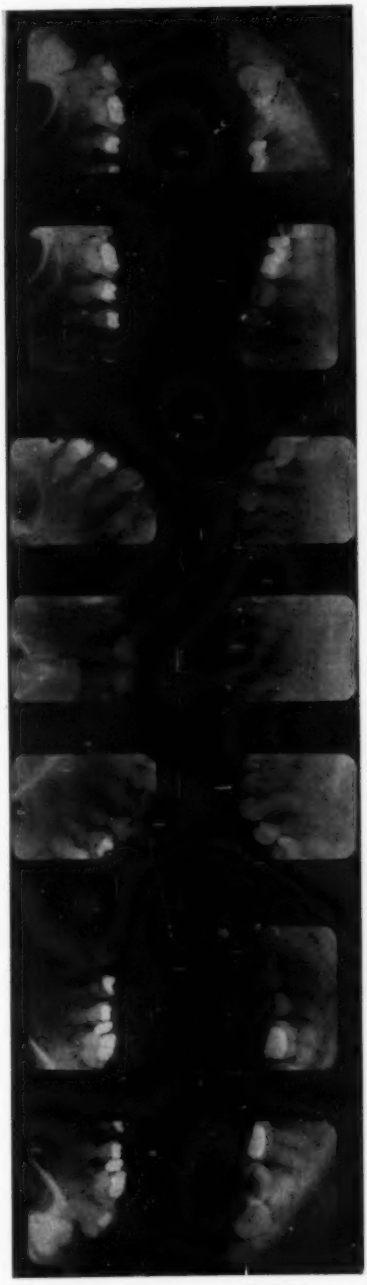

Fig. 3.—Same patient as in Fig. 2. Roentgenograms showing over-all decrease in size of teeth, short and spiky roots, with partial or complete obliteration of pulp chambers. Note several carious teeth without apparent periapical pathosis.

Family C.—The genealogic history of this family is illustrated by chart II, Fig. 5. Among 54 known members of the family, 27 were affected by this condition. Of the 27, 12 were males and 15 were females. Again, no sibling had the defect unless one of the parents had the malady. The clinical and roentgenographic findings of the presenting patient from this family were typical of hereditary dentinogenesis imperfecta.

Family L.—The pedigree of family L is represented by chart III, Fig. 6. The defect could be traced back four generations. Among 18 known members, the defect was present in 5 males and 4 females. The clinical characteristics of the disease are evident from Fig. 7 which shows the teeth of the patient from this family who was seen at the dental school. In addition, there were hypoplastic defects of the enamel in the upper and lower central incisor

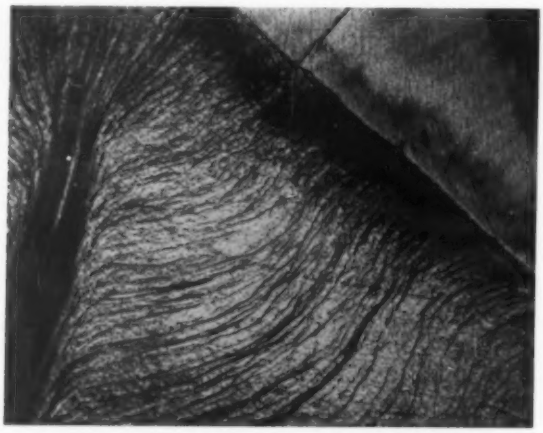

Fig. 4.—Photomicrograph of ground section of tooth showing lack of scalloping at the dentino-enamel junction. Note irregular and sparse branching of dentinal tubules.

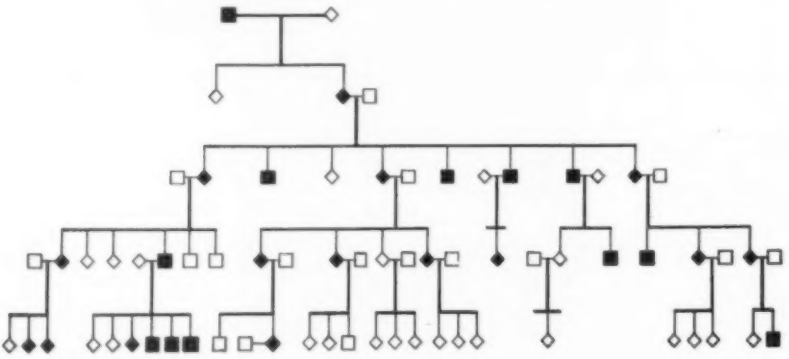

CHART II—PEDIGREE OF FAMILY C. SHOWING OCCURRENCE OF DENTINOGENESIS IMPERFECTA.

Fig. 5.

teeth. The roentgenograms were typical also of hereditary dentinogenesis imperfecta. The roots were spiked and the cervices were markedly constricted. The root canals were nearly obliterated in all the teeth, and the periodontal ligament seemed to be thickened.

According to Ivanciе[10] and Hursey and his colleagues,[11] the primary odontoblasts only form the peripheral part of the dentine and then degenerate. The remaining dentine is formed by odontoblastlike cells which are differentiated from the mesenchymal tissue. These cells are said to have a limited capacity to form a fully organized dentinal matrix. The process of differentiation of these cells and subsequent degeneration continues until the pulp cavity is partially or fully obliterated. Many teeth which appear to have obliterated canals radiographically actually have small canals present when sectioned.

SUMMARY AND CONCLUSIONS

A review of the literature and a genealogic, clinical, roentgenographic, and histopathologic study of hereditary dentinogenesis imperfecta in some members of three families and in a child with an unknown family history have led to the following conclusions:

1. The hereditary factor responsible for this anomaly is probably a non-sex-linked dominant factor.

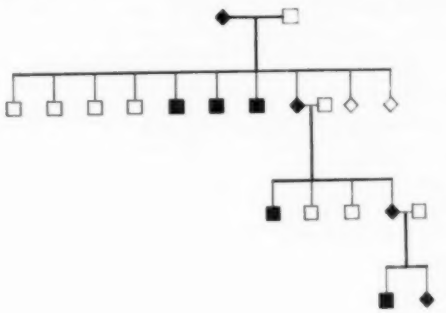

CHART III — PEDIGREE OF FAMILY L. WITH DENTINOGENESIS IMPERFECTA.

Fig. 6.

Fig. 7.—*Family L.*—Photograph of teeth showing typical features of the anomaly. Also note the hypoplasia of upper anterior teeth.

2. There is no definite correlation between this condition and systemic disorders such as nutritional deficiencies, blood dyserasias, infectious diseases, or metabolic disturbances. Cases of osteogenesis imperfecta associated with opalescent dentine have been reported but the exact relationship in their mode of transmission is not well understood since each condition may also occur independently.

3. Both deciduous and permanent dentitions are affected by dentinogenesis imperfecta. Occasional cases are on record in which only some of the teeth were involved and in which the distribution of abnormal dentine was of limited extent. The authenticity of such cases is not certain.

4. The malady is primarily limited to dentine. Enamel may be thin but is normal in other respects. The early loss of enamel is presumably due to the defective dentino-enamel junction.

5. The tendency to obliterate the pulp chamber and root canals by defective secondary dentine is not entirely in response to attrition, since unerupted teeth also exhibit the reduced pulp cavity. It could be due to abnormal activity of odontoblasts.

6. No unusual tendency toward the development of periapical pathosis or resistance to dental caries was evident in the cases in this series.

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THE RELATIONSHIP OF PERIANAL DERMATITIS TO FECAL pH

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PERIANAL dermatitis is a common condition during the neonatal period. Attention was first drawn to this fact by Pratt,[1] who found it in over 35 per cent of 289 white infants receiving cow's milk feedings. The incidence of this affection in a subsequent study by Pratt and Read[2] was reported as varying from 6.7 per cent to 22.5 per cent, depending on the race of the infant as well as on the type of feeding employed.

In 1955, when a new type of infant formula, Lactum, was introduced into one of our nurseries, our interest in the problem of perianal dermatitis led us to undertake a study of the new feeding preparation. Since determinations of the pH of the infants' stools were included in the observations, the opportunity arose for delineation of the possible relationship of perianal dermatitis to fecal acidity or alkalinity. A total of 1,505 infants was included in the study. Determinations of the pH of stools were made on 434 of these infants.

PLAN OF STUDY

Two nurseries in the private obstetrical pavilion were selected for the study. Only healthy infants weighing 2,500 grams or over were admitted to the nurseries. All of the babies in the study were white infants. Observations were carried out over a period of two years. During the first year, all of the infants in one nursery (PP2) received the standard diluted evaporated milk formula containing dextrimaltose in 5 per cent concentration. The caloric value of the formula was 65 per 100 ml. All of the infants in the second nursery (PP4) received an isocalorie Lactum formula. During the second year, formulas were switched so that infants in the PP2 nursery were fed the evaporated milk formula.

The routine of feeding the infants was the same in each nursery. On the first day of life, feedings were instituted after an initial period of starvation of 8 hours. Fifteen milliliters of 5 per cent dextrose in water were then given at 4-hour intervals for three feedings. This was followed by 15 ml. of the designated formula every 4 hours for a period of 24 hours. Each day thereafter the feedings were increased by 15 ml. until a maximum of 120 ml. per feeding was attained.

Although an effort was made to control the factor of faulty nursing care in the etiology of perianal dermatitis, unavoidable changes in nursing personnel added a variable which could not be eliminated. As an example of the difficulty, it may be pointed out that the supervisory nurses in each nursery were the same throughout but their period of active supervision was limited to the daytime hours. Changes

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in personnel working at other times inevitably raised doubts regarding the degree of adherence to the prescribed techniques.

Table I. Body Weights and Frequency of Stools of Infants Fed Two Types of Feeding

TYPE OF FEEDING	NUMBER OF INFANTS	AVERAGE INITIAL WEIGHT (GM.)	AVERAGE LOWEST WEIGHT (GM.)	AVERAGE WEIGHT ON EIGHTH DAY (GM.)	AVERAGE NUMBER OF STOOLS ON FOURTH DAY	AVERAGE NUMBER OF STOOLS ON EIGHTH DAY
Lactum	319	3,265	3,100	3,125	3.5	3.6
Diluted evaporated milk with 5 per cent dextrimaltose	362	3,180	3,040	3,065	4.1	4.2

Observation during the first year included comparison in the two groups of infants of weight gains, number and character of stools, and variability of pH of representative stool samples. The pH studies were continued during the second year. Daily inspection of the buttocks area was carried out by each shift of nurses in order to effect prompt treatment of the condition.

Determinations of pH of the stools were carried out by means of a Beckman Model G pH meter equipped with a Beckman glass electrode type 42. The stools were removed from the diapers a few minutes after passage by the infants. The pH was determined by application of the electrode to a portion of the fecal material.

RESULTS

Data indicating the weight gains and frequency of stools of 681 infants divided into two groups, the one receiving Lactum and the other, a standard evaporated milk formula, are listed in Table I. It will be noted that the figures are closely comparable in the two groups.

The over-all incidence of perianal dermatitis during the 2-year period is recorded in Table II. Of 729 infants receiving Lactum, 53 were found to have perianal skin changes, an incidence of 7.3 per cent. These figures may be compared with those found in the group of 776 infants fed the evaporated milk mixture. Among these there were 54 cases of perianal dermatitis, an incidence of 6.9 per cent.

Table II. Total Incidence of Perianal Dermatitis

TYPE OF FEEDING	NUMBER OF INFANTS	NUMBER OF CASES OF PERIANAL DERMATITIS	PER CENT
Lactum	729	53	7.3
Diluted evaporated milk with 5 per cent dextrimaltose	776	54	6.9

The experience gained by interchange of formulas in the two nurseries during the second year of the study is recorded in Tables III and IV. It may be seen that the feeding of Lactum in one nursery during the first year resulted in the appearance of 37 cases of perianal dermatitis, an incidence of 11.6 per cent. When the same formula was employed in another nursery during the second year, the skin affection appeared in 16 cases, representing 3.9 per cent of the

babies. Similar switching of evaporated milk feedings from one nursery to another was followed by the occurrence of 27 cases of dermatitis each year, the percentage incidence being 6.5 and 7.5, respectively. While the lowered incidence of perianal dermatitis following switching of Lactum feedings from one nursery to another tial. Although the tests were regularly carried out promptly after evacuation by the infants, the change in pH resulting in stools after being allowed to remain in the diaper 4 hours at room temperature was subjected to study. The results are recorded in Table V. In a total of 18 tests the stools were found in 10 instances to

TABLE III. INCIDENCE OF PERIANAL DERMATITIS IN TWO DIFFERENT NURSERIES IN INFANTS FED LACTUM

YEAR	NURSERY	NUMBER OF INFANTS	NUMBER OF CASES OF PERIANAL DERMATITIS	PER CENT
1955	PP4	319	37	11.6
1956	PP2	410	16	3.9

TABLE IV. INCIDENCE OF PERIANAL DERMATITIS IN TWO DIFFERENT NURSERIES IN INFANTS FED EVAPORATED MILK FORMULA

YEAR	NURSERY	NUMBER OF INFANTS	NUMBER OF CASES OF PERIANAL DERMATITIS	PER CENT
1955	PP2	414	27	6.5
1956	PP4	362	27	7.5

TABLE V. CHANGE IN pH OF STOOLS AFTER STANDING 4 HOURS AT ROOM TEMPERATURE

DAY OF LIFE OF INFANTS	NUMBER OF CASES WITH INCREASING ACIDITY	MEAN CHANGE IN pH*	NUMBER OF CASES WITH DECREASING ACIDITY	MEAN CHANGE IN pH*
1	1	−0.03		
2	1	−0.14	1	+0.09
3	2	−0.07	2	+0.32
4	4	−0.07	2	+0.34
5			2	+0.14
7	1	−0.26	1	+0.19
8	1	−0.41		

*Over-all mean change in pH was +0.04.

appeared to indicate a significant reduction, the figures obtained by the comparable maneuver in the case of evaporated milk failed to reveal an appreciable difference.

pH STUDIES

As a prerequisite to an attempt to relate fecal acidity and alkalinity to the appearance of perianal dermatitis, certain studies were considered essen- show a decrease in pH ranging from −0.03 to −0.41, the mean being −0.12. On the other hand, 8 specimens studied showed an increase in pH with a range of from +0.09 to +0.45, a mean of +0.24. The over-all mean change in pH was found to be +0.04.

In order to determine the error inherent in testing the pH of a random sample of stool, a series of 65 stool specimens was studied in which the

measurement of the pH of each stool was carried out twice, each time on a different portion of the fecal material. The results are recorded in Table VI. The range of difference in pH in the two tests varied from 0.02 to 0.45. The over-all mean variability of pH was found to be ±0.14, with a standard deviation of 0.09.

when the stools consisted of meconium, the pH tended to be at, or close to, its highest value, after which the figures tended to indicate increasing degrees of acidity. The mean pH for 126 infants 4 days of age and older in the evaporated milk group was 5.8, whereas for 110 infants in the Lactum group it was 5.65.

TABLE VI. VARIABILITY OF pH OF DIFFERENT PORTIONS OF SAME STOOL TESTED IMMEDIATELY AFTER EVACUATION

DAY OF LIFE OF INFANT	NUMBER OF CASES	MEAN pH OF STOOLS*	RANGE OF DIFFERENCE OF pH IN 2 TESTS OF SAME STOOL	MEAN VARIABILITY OF pH*
1	2	6.23	0.11-0.20	±0.15
2	10	6.10	0.02-0.33	±0.16
3	19	5.73	0.02-0.40	±0.19
4	9	5.93	0.01-0.25	±0.10
5	14	6.21	0.02-0.45	±0.14
6	8	5.60	0.05-0.31	±0.14
7	2	5.42	0.03-0.16	±0.09
8	1	7.69	0.19	±0.19

*Standard deviation of mean was 0.09.

TABLE VII. pH OF STOOLS OF INFANTS RECEIVING EVAPORATED MILK MIXTURE

	DAY OF LIFE								TOTAL NUMBER OF INFANTS
	1	2	3	4	5	6	7	8	
Number of infants	20	39	46	46	28	27	20	5	231
Mean pH*	6.26	6.11	5.89	5.89	5.49	5.86	5.54	6.04	
Range	5.75-8.82	5.12-7.90	4.58-7.11	4.99-7.20	4.81-6.70	4.81-6.70	4.73-7.60	4.89-6.50	

*Mean pH of infants 4 days of age and older (126 cases) was 5.80.

TABLE VIII. pH OF STOOLS OF INFANTS RECEIVING LACTUM

	DAY OF LIFE								TOTAL NUMBER OF INFANTS
	1	2	3	4	5	6	7	8	
Number of infants	16	38	39	40	35	22	9	4	203
Mean pH*	6.32	5.88	5.85	5.89	5.15	5.84	5.72	6.33	
Range	5.75-7.58	5.09-6.68	4.91-7.10	4.81-7.78	4.70-7.85	4.75-7.60	5.01-6.80	5.49-6.89	

*Mean pH of infants 4 days of age and older (110 cases) was 5.65.

Determinations of the pH of stools were carried out in 434 instances on samples obtained from both groups of infants during the 2-year period of observation. The mean values as well as the range of pH are given in Tables VII and VIII. On the first day of life,

A limited number of observations was made on the stools of infants at the time of development of perianal dermatitis. They were carried out on 13 infants between the third and seventh days of life. The values obtained were compared with those

found by testing the stools of infants of the same age and on the same diet who presented no abnormality of perianal skin. The results are listed in Table IX. It may be noted that in 8 infants receiving Lactum, perianal dermatitis developed at a time when the pH of the stools varied from 4.98 to 6.41, the mean figure being 5.45. These values may be compared with those found in 96 normal controls of the same ages who excreted stools with pH values ranging from 4.70 to 7.85, the mean being 5.60. In 5 infants fed an evaporated milk mixture, the appearance of perianal dermatitis coincided with the excretion of stools with pH values of from 4.99 to 7.10, the mean pH being 5.99. Control figures obtained from 75 infants were 4.73 to 7.60, with a mean of 5.64.

TABLE IX. pH OF STOOLS OF INFANTS WITH PERIANAL DERMATITIS COMPARED WITH NORMAL CONTROLS OF SAME AGE

TYPE OF FEEDING	CONDITION OF SKIN	NUMBER OF CASES	pH RANGE	MEAN pH
Lactum	Perianal dermatitis	8	4.98-6.41*	5.45*
	Normal	96	4.70-7.85	5.60
Diluted evaporated milk with 5 per cent dextrimaltose	Perianal dermatitis	5	4.99-7.10*	5.99*
	Normal	75	4.73-7.60	5.64

*pH determinations of stools at time of appearance of perianal dermatitis.

DISCUSSION

It has been known since the turn of the century that the stools of breast-fed infants are acid when tested with litmus and that those eliminated by infants receiving cow's milk tend to be alkaline. The early studies were supported by those of later investigators who tested the pH colorimetrically on dialyzates of stool samples. Thus, Ylppö[3] found the pH of the stools of breast-fed infants to vary from 4.6 to 5.2, whereas the values indicated on his charts for infants receiving cow's milk fell in the range of from 6.3 to 8.2. Tisdall and Brown[4] reported that in 1,300 determinations made on the stools of artificially fed infants the range of pH fell between 4.6 and 8.3. According to these authors, feeding of the usual cow's milk formulas in normal infants resulted in stools more alkaline than pH 7.0. The highly acid values were found in artificially fed infants only when severe diarrhea was present. More recently Barbero and co-workers[5] carried out an investigation of 236 infants of 2 weeks to 3 months of age, of whom 22 were fed human milk while the remainder were on diets consisting of standard evaporated milk mixtures supplemented with dextrimaltose or one of several commercial preparations with chemical compositions approaching that of human milk. The average pH of the stools of the breast-fed infants was found to be 5.5, with a range of from 4.3 to 7.5. In the case of infants receiving evaporated milk formulas, the average pH of the stools was found to be 6.7 and the range of values from 4.7 to 8.8. When other types of feedings were employed, average values of from 5.6 to 6.55 were obtained. The over-all range of pH when the special

formulas were employed was from 4.4 to 8.6. In their investigations, which included studies of the changing bacterial flora at different levels of small and large bowel, Barbero and his colleagues found that the acidity of the intestinal contents in breast-fed infants rapidly increases in the colon, presumably as a result of the fermentative activity of *Lactobacillus bifidus* and related microorganisms. By contrast, pH levels of from 6.0 to 8.0 which were found in the contents of the small bowel of all infants tended to remain unchanged in the large intestine when the diet consisted of cow's milk. As a result of the work of many investigators, it has been generally concluded that fecal acidity is influenced by a number of dietary factors, including the amount of protein and the type of carbohydrate ingested.[6] It has also been suggested that the bacterial flora and, in consequence, fecal acidity are influenced by the inhibitory action of certain fatty acids present in both human and cow's milk.[7]

Because perianal dermatitis constitutes an especially important problem during the first 2 weeks of life, it is of interest to review the available information regarding fecal acidity and alkalinity during this period. Here the numbers of infants studied and the published data are somewhat limited. In the series reported by Tisdall and Brown[4] there were data obtained from 12 breast-fed infants under 2 weeks of age. The range of fecal pH was reported as from 4.7 to 5.1. Norton and Shohl[8] carried out a careful study of 27 infants of whom 21 were exclusively breast fed. The results they obtained during the first 10 days from an average of approximately 12 daily determinations indicated that the mean pH of the stools fell slowly from the average figure of 6.08 (range 5.8 to 6.4) on the first day to 4.88 on the tenth day. The over-all range of values for the entire period was found to be from 4.3 to 6.6. Dods[9] analyzed the stools of 15 breast-fed infants. The average pH during the first 3 days of life was found to be 7.2. This value fell to 6.17 for the age period of 7 to 9 days, inclusive. Pratt and Read,[2] basing their study for the first time on the results obtained by employing a glass electrode for potentiometric determination of fecal pH, found average values in 1- to 3-day-old breast-fed infants of 6.4 (range 4.4 to 8.6), falling in older infants to 5.7 (range 4.4 to 7.6). When evaporated milk, dextrimaltose formulas were employed, the average pH of the stools of 31 1- to 3-day-old infants was found to be 6.3, with a range of from 5.1 to 8.0. After the third day, the average pH was 6.2, with a range of 4.7 to 7.7. These figures were compared with those found in 34 infants who received a formula chemically simulating that of human milk. Here the average pH during the first 3 days was 6.1, with a range of 4.7 to 7.0, while after this period the average was 5.8, with a range of from 4.9 to 7.0.

Pratt and Read were of the opinion that the mean pH values in the 3 groups during the first 3 days of life, 6.4, 6.3, and 6.1, respectively, indicated little. On the other hand, they believed that the differing mean values found after the third day, 5.7 for breast-fed infants, 6.2 for those receiving evaporated milk, and 5.8 for those receiving simulated human milk, could be correlated with the differing

incidence of perianal dermatitis in these groups of infants. The figures which they reported for the incidence of the skin affection were 7.1 per cent for breast-fed infants, 19.7 per cent for those fed evaporated milk mixtures, and 14.0 per cent for those receiving the simulated human milk formula. These authors concluded that the frequency of the disease varied with the pH of the stool and of the perianal skin, being least frequent the more acid the stool and the perianal skin.

The results of the present study point to an increase in the acidity of the stools in both groups of infants after the first day of life. The degree of acidity as measured by mean values was less than that found in breast-fed infants by Tisdall and Brown and by Norton and Shohl but differed little from the figures obtained with the glass electrode by Pratt and Read. Nevertheless, it would appear to be hazardous to place much stress on mean values in the face of the great variability of the individual values. Thus, beginning with the third day, the range of variation was such that the most marked acidity of the stools was usually below pH 5.0 while the greatest degree of alkalinity on several days was above pH 7.5. The fact that there was considerable divergency in the results obtained when pH determinations were made on different samples of the same stool specimen poses additional difficulties in interpretation.

The general incidence of perianal dermatitis in the present study, approximately 7 per cent, was the same as that reported by Pratt and Read for breast-fed infants but was sharply lower than the figures they reported in infants receiving cow's milk formulas. A high figure of 11.6 per cent was obtained in one of the nurseries during one year when the infants were fed a Lactum formula. The drop in incidence to 3.9 per cent when the same formula was subsequently used in another nursery suggested that perhaps the quality of nursing care was the determining factor which favored the greater or lesser incidence of the dermatitis.

A comparison of the acidity of the stools in infants who developed perianal dermatitis with that found in normal control infants of the same age gave little support to the thesis that an alkaline pH is accountable for the condition. Several of the infants excreted markedly acid stools at the time when the dermatitis appeared. Moreover, the ranges of pH observed as well as the mean values were similar in the cases with and without dermatitis. One is led to share the general impression that fecal material is potentially irritating to the skin of the newborn infant and that its effects become more pronounced the longer a soiled diaper remains in contact with the perianal skin area. That the deleterious effect of prolonged contact of feces with the skin is not exerted through progressive alterations in the pH of the evacuated material is suggested by the absence of consistent changes in acidity of feces allowed to remain in the diaper for 4 hours.

SUMMARY

Perianal dermatitis is a common skin affection in the neonatal period. In a study carried out over a 2-year period on 1,505 infants fed two evaporated milk preparations, 107 cases of

perianal dermatitis were observed, an incidence of 7.1 per cent. In different nurseries and at different times, feeding of the same formula was followed by a sharply varying incidence in appearance of the condition. Data obtained from measurements of the pH of the stools in 434 cases failed to support the thesis that fecal alkalinity is a major factor in the genesis of perianal dermatitis.

We are indebted to Dr. Martin C. Ushkow for assistance in the gathering and for analysis of some of the data.

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MORTALITY EXPERIENCE AMONG CHILDREN WITH CONGENITAL MALFORMATIONS

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DEATHS attributed to congenital malformations constitute a significant portion of infant and neonatal mortality. For example, in New York City approximately 15 per cent of all neonatal deaths have been attributed on death certificates to this cause alone. Furthermore, the percentage of infant and neonatal deaths attributed to congenital malformations over the past decade has remained relatively stationary in New York City. It is evident that, until further research efforts result in a more complete understanding of the etiology and prevention of congenital malformations, emphasis must be placed upon early diagnosis, prompt treatment, and rehabilitation. While it is recognized that the primary responsibility for early diagnosis, treatment, and rehabilitation must rest with those physicians delivering babies or caring for them throughout the period of infancy and childhood, the significant role played by congenital malformations in mortality and morbidity constitutes a considerable public health problem.

This study was undertaken to secure data to answer the following questions: (1) Are any deaths attributed to congenital malformations preventable? (2) If so, what is the extent and what are the preventable factors?

In order to provide answers to the above questions, a study was undertaken of all deaths of persons under 20 years of age attributed to congenital malformations on death certificates in New York City in 1954.

METHOD OF STUDY

1. All death certificates for individuals under 20 years of age in which death was attributed to a congenital malformation in 1954 were reviewed.

2. A study form was devised for the uniform abstracting of data.

3. A group of pediatricians reviewed the hospital charts at the hospital of death of all 20-year-old and younger persons whose deaths were attributed to congenital malformations on the death certificate. At the time of the review, the data on the hospital charts were abstracted on to the study form.

4. After the review of the hospital charts, the case register of the handicapped children's program was searched for the individual deaths. Where a child had been known to the program, the program chart was also reviewed and data abstracted onto the study form.

From the University of Minnesota School of Public Health.

With the field assistance of Lloyd Thomas, M.D., Charlotte B. Lissauer, M.D., and Bina Sawyer, M.D., and the statistical assistance of Herbert Rich, M.A.

Presented at the Postgraduate Institute, Medical Faculty, University of Minnesota.

TABLE I. CAUSE OF DEATH (ON HOSPITAL CHART) AND AGE AT DEATH

DIAGNOSIS	TOTAL	AGE						
		UNDER 1 DAY	1 TO 27 DAYS	1 TO 11 MONTHS	1 TO 4 YEARS	5 TO 9 YEARS	10 TO 14 YEARS	15 TO 19 YEARS
1 Heart Disease	252	10	99	104	28	7	3	1
Only	195	8	83	79	18	5	1	1
With Monogolism	24	—	4	12	6	1	1	—
With minor condition	33	2	12	13	4	1	1	—
2 Central Nervous System	160	58	28	56	17	—	1	—
Anencephaly	39	29	9	1	—	—	—	—
Spina bifida (only)	4	1	1	1	1	—	—	—
Spina bifida (with hydrocephalus)	10	5	2	3	—	—	—	—
Spina bifida (with meningocele)	6	—	3	3	—	—	—	—
Spina bifida (with hydrocephalus and meningocele)	7	—	1	3	3	—	—	—
Hydrocephalus (only)	49	15	5	23	5	—	1	—
Hydrocephalus (with meningocele)	19	1	2	11	5	—	—	—
Other central nervous system disorders	8	3	2	2	1	—	—	—
Meningocele, meningomyocele	18	4	3	9	2	—	—	—
3 Gastrointestinal	94	5	48	20	15	5	—	1
Pyloric stenosis	4	—	—	4	—	—	—	—
Imperforate anus	15	4	7	4	—	—	—	—
Atresia of duodenum	7	—	6	1	—	—	—	—
Atresia of rest of gastrointestinal tract	17	1	9	4	3	—	—	—
Tracheoesophageal fistula	18	—	16	1	1	—	—	—
Atresia of bile duct	3	—	—	—	3	—	—	—
Malrotation of gastrointestinal tract	11	—	7	4	—	—	—	—
Cystic fibrosis pancreas	19	—	3	2	8	5	—	1
4 Genitourinary	32	15	6	5	3	—	—	3
Polycystic kidney	15	10	3	2	—	—	—	—
Obstruction of genitourinary tract	7	1	1	1	2	—	—	2
Other genitourinary disorders	10	4	2	2	1	—	—	1
5 Cleft Palate	10	2	2	3	3	—	—	—
6 Multiple	36	12	15	6	2	—	—	1
7 Miscellaneous	45	11	19	10	2	1	2	—
Totals	629	113	217	204	70	13	6	6

THE STUDY GROUP

A total of 857 deaths attributed to congenital malformations was reported in New York City in 1954. Of this number, 109 (12.7 per cent) occurred in people 20 years and over and were automatically excluded from the study; 53 (6.2 per cent) occurred at home and were excluded from the study; in 24 (2.8 per cent) the hospital chart could not be located during the course of the study; the records of 13 (1.5 per cent) were not reviewed; upon investigation 29 deaths (3.4 per cent) were found not to be due to a congenital malformation. The study is composed of the remaining 629 deaths (73.4 per cent).

CAUSE OF DEATH AND AGE AT DEATH

Table I and Fig. 1 show the data on cause of death (as stated on hospital charts) and age of death in the 629 children studied. Of the 629 deaths, 252 (40 per cent) were attributed to heart disease; the great majority of these children had heart disease only, with only 20 per cent having an associated condition. Most of the deaths due to heart disease (85 per cent) occurred in the first year of life and 43 per cent occurred within the neonatal period.

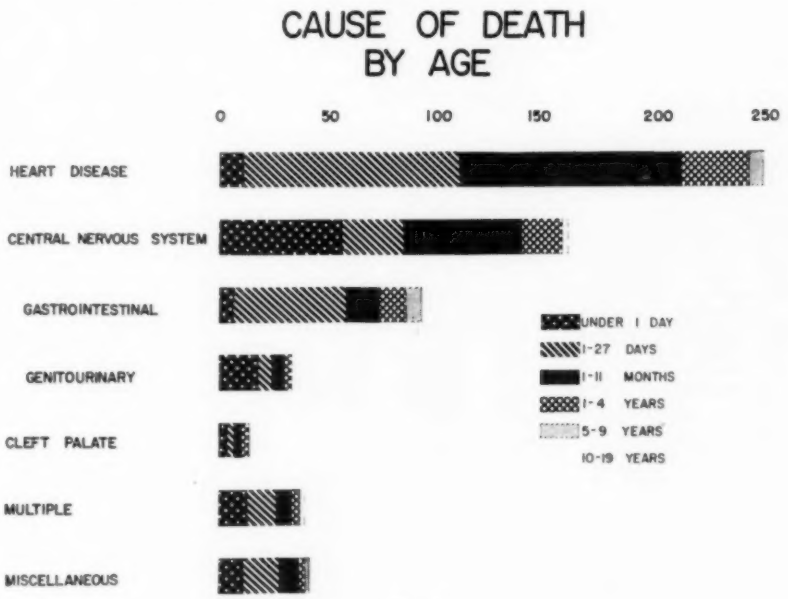

Fig. 1.

One quarter of the deaths (160) were attributed to central nervous system conditions, the most frequent being hydrocephalus, anencephaly, spina bifida, and meningocele. Of these 160 deaths, slightly over one half occurred within the neonatal period and 35 per cent in the postneonatal period.*

*From the twenty-eighth day of life to the first birthday.

Fifteen per cent of the deaths (94) were attributed to gastrointestinal conditions, the most frequent being cystic fibrosis of the pancreas, tracheoesophageal fistula, atresia of the gastrointestinal tract, and imperforate anus. Slightly over one half of these deaths occurred within the neonatal period and 21 per cent in the postneonatal period.

Five per cent of the deaths were attributed to conditions of the genitourinary system, the most frequent type being polycystic kidney. Seventy per cent of these deaths occurred within the neonatal period.

TABLE II. CAUSE OF DEATH

	HOSPITAL CHART	TOTAL	DEATH CERTIFICATE									
			MONSTROSITY	SPINA BIFIDA AND MENINGOCELE	HYDROCEPHALUS	OTHER CENTRAL NERVOUS SYSTEM DISORDERS	CIRCULATORY	CLEFT PALATE	DIGESTIVE	GENITOURINARY	BONE AND JOINT	OTHER
10	Anencephaly	39	36	2	1	—	—	—	—	—	—	—
20	Spina bifida (only)	4	—	3	1	—	—	—	—	—	—	—
21	Spina bifida (with hydrocephalus)	10	1	3	6	—	—	—	—	—	—	—
22	Spina bifida (with meningocele)	6	—	6	—	—	—	—	—	—	—	—
23	Spina bifida (with hydrocephalus and meningocele)	7	—	5	2	—	—	—	—	—	—	—
30	Hydrocephalus (only)	49	—	5	41	1	1	—	—	—	1	—
31	Hydrocephalus (with meningocele)	19	—	13	6	—	—	—	—	—	—	—
32	Other central nervous system disorders	8	1	—	—	5	2	—	—	—	—	—
40	Heart disease (only)	195	1	—	—	2	189	—	2	—	—	1
41	Heart disease (with Mongolism)	24	—	—	—	—	22	—	2	—	—	—
42	Heart disease (with minor conditions)	33	—	—	1	—	27	1	1	—	—	3
50	Cleft palate	10	—	—	—	—	3	5	—	—	—	2
60	Pyloric stenosis	4	—	—	—	—	—	—	4	—	—	—
61	Imperforate anus	15	—	—	—	—	—	—	11	1	—	3
62	Atresia of duodenum	7	—	—	—	—	—	—	7	—	—	—
63	Atresia of rest of gastrointestinal tract	17	—	—	—	—	—	—	17	—	—	—
64	Malrotation of gastrointestinal tract	11	—	—	—	—	—	—	11	—	—	—
65	Tracheoesophageal fistula	18	—	—	2	—	1	—	14	—	—	1
70	Polycystic kidney	15	—	—	—	—	—	—	—	12	—	3
72	Obstruction of genitourinary tract	7	—	—	—	—	—	—	—	5	—	2
73	Other genitourinary disorders	10	1	1	—	1	—	—	—	7	—	—
80	Cystic fibrosis pancreas	19	—	—	—	—	—	—	18	—	—	1
81	Atresia of bile duct	3	—	—	—	—	—	—	3	—	—	—
82	Meningocele, meningomyocele	18	1	15	—	—	—	—	—	—	1	1
98	Miscellaneous	45	—	1	1	1	8	1	16	2	2	14
99	Multiple	36	2	3	4	3	2	—	9	3	2	8
	Totals	629	43	57	65	13	255	6	115	30	6	39

There were 10 deaths attributed to cleft palate, of which 4 occurred in the neonatal period and 3 in the postneonatal period.

Thirty-six deaths (6 per cent) were attributed to multiple malformations; most of these deaths occurred within the neonatal period.

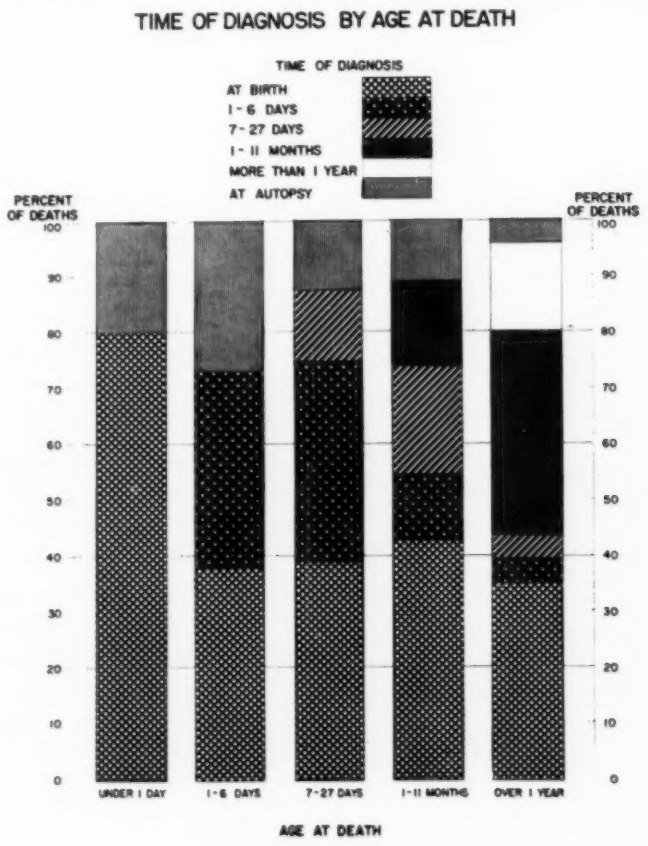

Fig. 2.

All together, 330 of the 629 deaths (52 per cent) occurred within the neonatal period, 204 (32 per cent) in the postneonatal period, 70 (11 per cent) in the preschool period, and 25 (4 per cent) in children of school age (Table I and Fig. 1).

COMPARISON OF CAUSE OF DEATH ON DEATH CERTIFICATE AND HOSPITAL CHART

Table II shows a comparison between the cause of death recorded on the death certificate with the cause of death recorded on the hospital chart at the hospital of death. It will be noted that, in general, there is a good correlation between the two sets of information regarding cause of death.

TIME OF DIAGNOSIS AND AGE OF DEATH

Fig. 2 shows the relationship between time of diagnosis and age of

death. It will be noted that, according to data noted on the hospital records in the deaths occurring after the first year of life, in 4 per cent of the deaths the diagnosis was not made until autopsy; in 16 per cent of the deaths the diagnosis was not made until after the child's first birthday; in 37 per cent of the deaths the diagnosis was not made until the postneonatal period of life. Comparable delays in diagnosis are evident from Fig. 2 in each of the other columns of age at death. Therefore it seems reasonable, to conclude that there is a significant factor of delay in diagnosis in this group of deaths.

INTERIM HOSPITAL CARE

Slightly over one half of the deaths occurred within the neonatal period, one third of the deaths in the postneonatal period, and one tenth of the deaths in the preschool period. Only small percentages occurred in older children.

Eighty-five per cent of the children who died had no interim hospital care (i.e., other than that at the place of birth and/or place of death). Six per cent visited one interim hospital and one per cent, two interim hospitals.

PREVENTABILITY

There was further analysis of the deaths to study the factor of preventability. Of the 629 deaths, the reviewers were of the opinion that 30 (4.8 per cent) were preventable* and that an additional 52 deaths (8.2 per cent) were probably preventable. The reviewers were of the opinion that 463 deaths (73.6 per cent) were not preventable. An additional 84 deaths (13.3 per cent) were considered probably unpreventable.

Of the 30 deaths considered preventable, one half occurred in the postneonatal period and almost one third in the neonatal period. Of the 52 deaths considered probably preventable, almost one half occurred in the postneonatal period, one third in the neonatal period, and one sixth in the preschool period. Of the 463 unpreventable deaths, 60 per cent occurred in the neonatal period, one third in the postneonatal period, and almost one tenth in the preschool period. Of the 84 deaths considered probably unpreventable, almost 40 per cent occurred in the neonatal and postneonatal periods and one fifth in the preschool period.

AUTOPSY STATUS

Table III shows the analysis of the deaths by autopsy. Of the entire group of 629 deaths, 410 (65 per cent) were autopsied.

CHILDREN KNOWN TO HANDICAPPED CHILDREN'S PROGRAM

Since 1945, the handicapped children's payment program in New York City has provided some services for children with congenital malformations. In the earlier years the types of congenital malformations covered by the program included primarily the musculoskeletal and cleft palate groups. In 1950 congenital heart disease was added to the list, and in 1953 the list of eligible congenital malformations was broadened to include all malformations of all systems which are amenable to surgery, or rehabilitation, or both.

*A preventable death is defined as one in which there was evidence that the management of the patient did not include any or all of the essential steps necessary to conserve life.

Table IV shows that 36 of the 629 children (6 per cent) were known to the handicapped children's program of the New York City Department of Health. When one considers that all of the diagnostic conditions listed are theoretically eligible for care under the program, it is evident that care under the program was requested for only a small percentage of the children. Possible reasons for this are: (1) a good proportion of the children died within the neonatal period; (2) the families of some children are able to pay for the care themselves; (3) the program did not include payment for conservative medical treatment.

TABLE III. AUTOPSY STATUS

DIAGNOSIS	TOTAL NUMBER	AUTOPSY STATUS			
		PERFORMED	NOT PERFORMED	UNKNOWN	AUTOPSIED (PER CENT)
Heart disease	252	175	76	1	69.4
Central nervous system	160	69	89	2	43.1
Gastrointestinal	94	72	22	-	76.6
Genitourinary	32	29	3	-	90.6
Cleft palate	10	5	5	-	50.0
Multiple	36	30	6	-	83.3
Miscellaneous	45	30	14	1	66.7
Totals	629	410	215	4	65.2

TABLE IV. CHILDERN KNOWN TO HANDICAPPED CHILDREN'S PROGRAM

DIAGNOSIS	TOTAL	KNOWN	NOT KNOWN	KNOWN (PER CENT)
Heart disease	252	17	235	7
Central nervous system	160	10	150	6
Gastrointestinal	94	3	91	3
Genitourinary	32	3	29	9
Cleft palate	10	0	10	0
Multiple	36	1	35	3
Miscellaneous	45	2	43	4
Totals	629	36	593	6

SUMMARY

This paper reports the findings of a study of deaths attributed to congenital malformations in children and youth in New York City in 1954. The significant findings are:

1. Five per cent of the deaths were considered preventable and an additional 8 per cent were probably preventable.

2. Forty per cent of the deaths were attributed to heart disease, 25 per cent to central nervous system conditions, 15 per cent to gastrointestinal conditions, 5 per cent to genitourinary conditions, 2 per cent to cleft palate, and 6 per cent to multiple malformations.

3. Fifty-two per cent of the deaths occurred in the neonatal period, 32 per cent in the postneonatal period, 11 per cent in the preschool period, and 4 per cent in the school-aged group.

4. There was good correlation of the data on cause of death from the death certificates and from the hospital records.

5. There was some evidence to indicate delay in diagnosis.

6. Sixty-five per cent of the patients who died were autopsied.

7. Six per cent of the children who died were known to the handicapped children's program of the New York City Department of Health.

CONCLUSIONS

The important fact in the foregoing analysis is that 5 per cent of the deaths

were considered to be preventable, with an additional 8 per cent considered probably preventable. In reviewing the diagnoses of the deaths, it seems likely that those diagnoses with the best chance of preventability are malformations of the gastrointestinal tract (pyloric stenosis, imperforate anus, atresia, tracheoesophageal fistula, malrotation), obstruction of the genitourinary tract, and cleft palate. Factors playing a part in preventability include time of diagnosis and the place of care at birth and death. Out of these facts emerges a series of possible steps which might be suggested on a community-wide basis for the reduction of mortality attributed to congenital malformations.

The first suggestion is that recommended by the American Academy of Pediatrics[1] for the appraisal of the newborn infant as soon after birth as possible and careful observation and supervision of the infants during their course in hospital newborn infant nurseries. The further implementation of these recommendations might facilitate earlier diagnosis of congenital malformations.

The second suggestion relates to the quality of hospital care and the pattern of usage of hospital facilities in a community. Certain hospitals within New York City are approved by the New York City Department of Health for payment for the care of handicapped children with certain diagnostic conditions. When a hospital applies for approval, the decision is made on the basis of certain criteria established by advisory committees. Since, at present, not all hospitals caring for children are approved, the questions to be raised lie in two main directions: (1) Is it possible to assist all hospitals within the community to meet the recommended minimum criteria? (2) If this is not possible, is it possible or feasible to encourage the transfer of children with certain conditions requiring specialized care to the approved hospitals of the community? It is recognized that these are knotty problems with no easy solution.

REFERENCE

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ACUTE TEMPORAL MYOSITIS

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ON OCCASION children have been seen with bilateral swellings of the temporal regions. The swellings were noted suddenly, were not tender, and were not associated with constitutional signs or symptoms. Histories revealed that these children had been chewing vigorously for prolonged periods just before the appearance of the swellings, which then disappeared within 24 hours.

Fig. 1.—M. M., showing bilateral temporal swellings.

The swellings appear over the origin of the temporal muscles where they arise from the temporal fossae, the other portions of the muscle being restricted beneath the zygomata. It has been suggested by Adams and associates[1] in discussing "shin splints" that the temporary myositis follows the liberation of excessive metabolites. Three cases are reported.

CASE REPORT

M. M., 3 years of age, was noticed by her parents to have a "swelling of her face" late one evening. She had been chewing a wad of bubble gum all day. Her photograph is shown.

R. H., 2½ years old, was seen with the previously mentioned swellings. She had eaten several small hard apples during the day. The swellings disappeared by the following morning.

T. R., 3 years of age, consumed a large candy cane, and within a few hours he developed the typical temporal swellings. By the following day the swellings had gone.

SUMMARY

Myositis of the temporal muscles may be caused by prolonged chewing. The condition is harmless and requires no treatment.

REFERENCE

1. Adams, R. D., Denny-Brown, D., and Pearson, Carl M.: Diseases of Muscle, New York City, 1953, Paul B. Hoeber, p. 394.

"No man undertakes a light task, in the present day of active and unceasing work, when he attempts to elucidate, or throw a further gleam of light upon, any topic in scientific or practical medicine; still, even the smallest fact is important, and is often the starting point of some great achievement in science. Every thoughtful investigator contributes to the general stock of knowledge, in however small a degree, and gives a fresh impetus to research. Great truths sometimes have their origin in great errors."

Transactions of William Henry Day, M.D., Ninth International Medical Congress, vol. 3, 1887.

GASTROTOMY FOR LACTOBEZOAR IN A NEWBORN INFANT

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THE use of commercial powdered milks in infant feeding has become a common practice. This report emphasizes a complication which can occur if there is a misunderstanding concerning the preparation of the formula.

CASE REPORT

An 18-day-old white girl, whose birth weight was 5 pounds, 9 ounces, was breast fed for about two weeks and did well. SMA (Wyeth) milk formula, 1:1, was then prescribed. She began to vomit within 24 hours.

At the end of 48 hours a 1:1½ dilution was made by the child's mother because of the vomiting. Two days later the child had liquid stools. She was returned to her physician who stopped the milk formula and prescribed clear liquids. The vomiting continued; one day later because of dehydration, her physician referred her to The Children's Hospital.

Physical Examination.—The infant was severely dehydrated; her weight was 5 pounds 3 ounces; the skin turgor was very poor; her fontanel and eyes were sunken. An abdominal mass was palpated in the upper part of the abdomen. It was hard and about one inch in width and 2½ inches long. The right lower abdominal quadrant felt empty, but a rectal examination was normal. On admission a diagnosis was made of intussusception with severe dehydration; fluids were administered and she was taken to the operating room where a transverse abdominal incision was made.* An ileocolic intussusception was found and easily reduced with slight digital pressure. In the left upper quadrant a hard solid mass was felt. The surgical incision was extended. The stomach was found to be distended and hard. It was opened and a solid milk curd cast filling the the entire lumen was removed. This cast did not extend beyond the pylorus. Fig. 1 demonstrates the lactobezoar in schematic sketch. The infant was taking oral feedings 30 hours after the operation and went home on the sixth postoperative day.

On questioning the mother further, it was learned that the 1:1 formula was originally mixed by adding one part of powdered formula to one equal part of water. She later diluted the formula somewhat by adding 1½ parts of water to one part of powdered milk.

DISCUSSION

The manufacturer of this powdered milk suggests that one level measuring cup of powder, which is supplied with the formula, be mixed with one ounce of water, a proportion which supplies a formula of 20 calories per ounce. The measuring cup holds approximately 7 c.c. of water.

In contrast, the liquid milk concentrate is to be diluted with equal parts of water. Both preparations,

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*Surgery by Dr. William Johnson, Pediatric Surgeon.

when properly mixed, supply 20 calories per ounce. Unless the form of the milk product to be used is specified, an error of the type reported here becomes quite possible. This child's incorrectly mixed formula contained approximately 85 calories per ounce. This concentrated formula was sucked through the nipple but appears to have become inspissated in the stomach. The ileocolic intussusception complicated the clinical picture but could scarcely be held accountable for the obstructing lactobezoar.

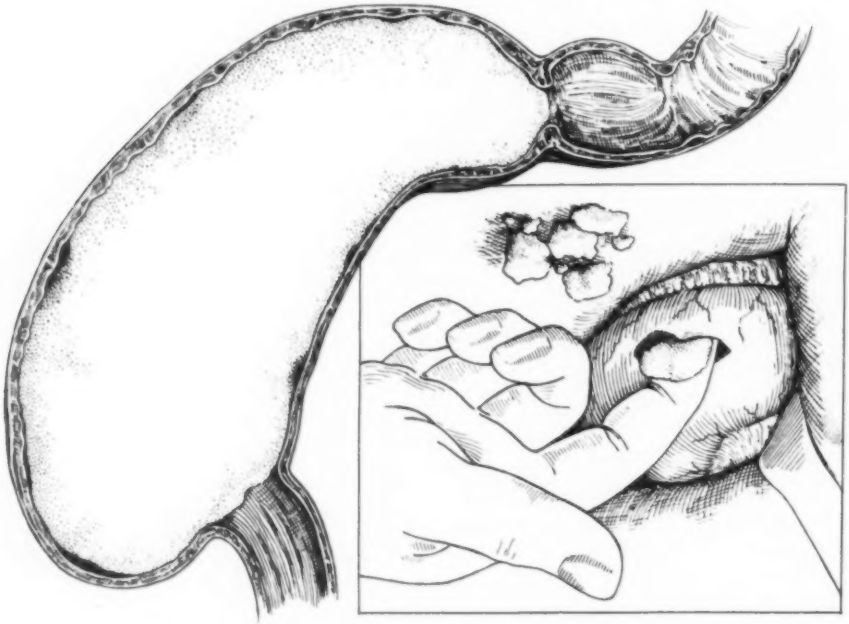

Fig. 1.—The solid lactobezoar is sketched as it appeared at surgery, filling the infant's stomach. Top left inset shows the surgeon's finger breaking up the bezoar and removing it. (Prepared by Audio-Visual Education Department, University of Louisville School of Medicine.)

SUMMARY

An instance of gastric obstruction in an infant by a lactobezoar produced by inspissated milk is recorded.

The lactobezoar apparently was related to the feeding of a hypercaloric milk formula.

INTESTINAL OBSTRUCTION DUE TO PROTEIN CASTS

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EXCEPT in veterinary medicine, where it receives first priority, abnormal contents of the intestinal tract are rarely considered in the differential diagnosis of intestinal obstruction. This is inexplicable since fecal impaction is probably the most common and the oldest recognized cause of obstruction. Meconium ileus is a well-recognized manifestation of cystic fibrosis of the pancreas.

A recent review which includes the postoperative prognosis of this type of obstruction is available.[1] Years ago Falls and Jaffe[2] pointed out that the anorectal plug or "meconium worm" is frequently the sole cause of intestinal obstruction in newborn infants. Since all newborn infants have (or have had) such a plug, a 12-hour period of observation following its removal is necessary before surgical exploration for a more serious disease is undertaken (provided that there is no evidence of compromised mesenteric circulation). Mechanical obstruction should still be suspected. It has been my experience that the plug is less likely to be expressed by newborn infants with atresia of the intestine (see Fig. 1, *A*).

Abnormalities in the meconium of the fetus and newborn infant were thoroughly covered in a recent paper by Emery,[3] and the clinical aspects outlined in cases reported by Zachary.[4] Obstruction and perforation may result from intestinal fecal casts as well as from classical meconium ileus[5] (see Fig. 1, *B*).

Levy,[6] in 1951, first reported a case of late fecal obstruction associated with cystic fibrosis of the pancreas in a 7-month-old infant. He emphasized the altered physical state of fecal contents which resulted in puttylike feces responsible for intestinal obstruction beyond the newborn period. More recent case reports and discussions of "late meconium ileus" are provided by Fisher,[7] Nixon,[8] Birse,[9] and Andersen.[10] Shwachman[11] emphasized that the obstructing material in the intestinal lumen may be either puttylike or hard and rocklike. I have been impressed with the combination of impactive obstruction and paradoxical diarrhea in these patients. Photographs of such specimens were taken but were not included because they cannot be distinguished from photographs of molding putty, new or dried out, and are familiar to all. (The father of one patient had often picked up pieces of this material from the floor and made models with it, thinking it was molding clay carelessly left around by his child.)

The following case history describes the results of another type of intraluminal cast. This 2-month-old infant with cystic fibrosis of the pancreas suddenly had his entire intestine obstructed by precipitated milk protein (see Fig. 1, *C*).

CASE REPORT

This patient was one of twins born to a 28-year-old mother. There were

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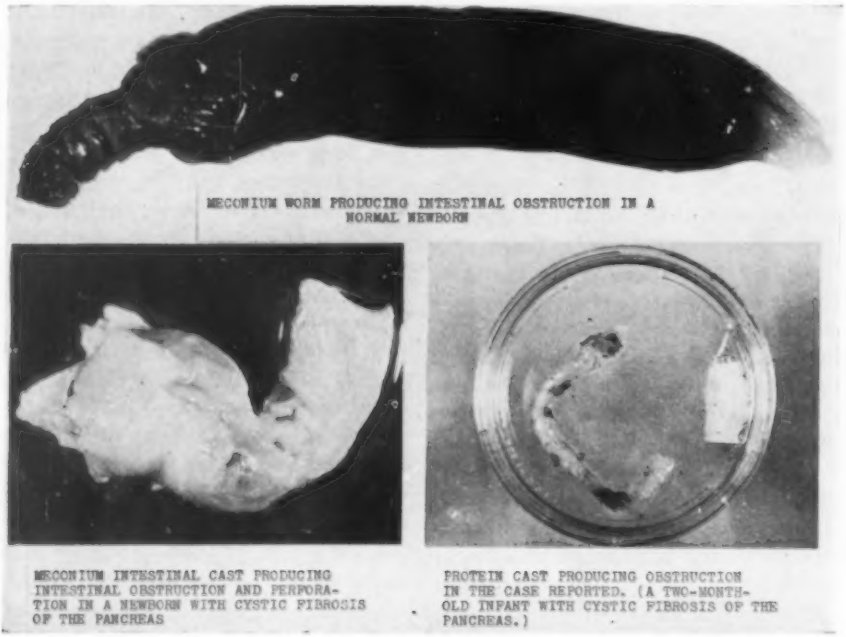
no siblings, and the family history was noncontributory. The twins were fed Bremil (Borden's) and had no particular difficulty during the first 2 months of life. However, because of too frequent stools, they were suddenly changed from Bremil to 13 ounces of evaporated milk and 13 ounces of water, with no added sugar, 48 hours before admission. One twin tolerated this formula, but the other began



MECONIUM WORM PRODUCING INTESTINAL OBSTRUCTION IN A NORMAL NEWBORN

MECONIUM INTESTINAL CAST PRODUCING INTESTINAL OBSTRUCTION AND PERFORATION IN A NEWBORN WITH CYSTIC FIBROSIS OF THE PANCREAS

PROTEIN CAST PRODUCING OBSTRUCTION IN THE CASE REPORTED. (A TWO-MONTH-OLD INFANT WITH CYSTIC FIBROSIS OF THE PANCREAS.)

Fig. 1.

vomiting, became listless and obviously uncomfortable. He had intermittent intestinal discomfort. He had no stools after the formula change. Five enemas produced only mucus.

The patient was admitted to Walter Reed Army Hospital on Jan. 26, 1956. His temperature was 101.4° F. He was well developed and well nourished but was quite listless. The abdomen was distended and difficult to examine, but dilated loops of bowel were evident. Occasional bowel sounds were heard. The rectosigmoid was empty. X-ray examination showed dilated loops of bowel, but no free air in the peritoneal cavity. White blood cell count was 7,700; differential, normal; platelet count, 64,000 per cubic millimeter; blood urea nitrogen, 15 mg. per cent; chloride, 98.4 mEq. per liter; carbon dioxide 15 mEq. per liter.

The diagnosis of intestinal obstruction was made, and an exploratory operation was performed. The abdomen was distended. When opened through a right paramedian incision, the intestines protruded immediately through the incision. The entire bowel appeared viable, and there was no obvious extraluminal cause for the obstruction. The proximal three fourths of the small intestine was greatly dilated. The distal third was contracted and filled with an opalescent material which looked and felt much like the white of a hard boiled egg. The colon was empty and collapsed. The operator attempted to milk the abnormal fecal material into the cecum

with only partial success. Because of the infant's general condition, further attempts were deemed contraindicated. The abdomen was therefore closed.

Postoperative duodenal drainage revealed only traces of tryptic activity and 0.6 per cent unit of lipase. The child passed pencil-sized fragments of what appeared to be coagulated protein. Microscopic appearance was reported as "amorphous material with no structural pattern." Fat stains showed only a small amount of fat. Chemical analysis revealed that this material contained 65.8 mg. of nitrogen per gram (427.7 mg. of protein per gram), 66 mg. of fat per gram, 15.5 mg. of calcium per gram, 0.15 mEq. of sodium per gram, and .065 mEq. of potassium per gram (dry weight). The low potassium compared with the sodium content suggests that this material at no time had the potassium-sodium ratio of 2:2 which is characteristic of living tissue. The protein composition was similar to that of evaporated milk.

TABLE I. SWEAT TESTS

AGE (MONTHS)	TWIN A		TWIN B	
	SODIUM	CHLORINE	SODIUM	CHLORINE
5	61.0	90	88	72
6	92.3	109	150	180
7	133.0	127	178	172
	Duodenal Drainage			
6	No trypsin		No trypsin	

The child remained obstructed in spite of the instillation of pancreatic granules through a duodenal tube. A reopening of the laparotomy was therefore performed. The abnormal intestinal contents were forcibly removed from the terminal ileum through an ileostomy and a decompression ileostomy tube was left in place. Except for a transient episode of hypokalemia, the postoperative course was uneventful.

Although there was no doubt that these children had pancreatic cystic fibrosis, both of them have done very well with only minor gastrointestinal and respiratory symptoms. The diagnosis was, in fact, questioned and the sweat tests were repeated at another institution when the twins were 1 year old. The tests were again characteristic of this disorder.

SUMMARY

1. A case of intestinal obstruction from a milk protein cast of the entire intestine is reported.

2. Although this is believed to be the first such report, its actual incidence in milder form in normal children as well as in infants with pancreatic fibrosis is open to speculation.

3. The latter part of this narrative also illustrates how asymptomatic cystic fibrosis of the pancreas may exist even when parents are aware of the diagnosis and are apprehensively searching for symptoms.

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LANDRY-GUILLAIN-BARRÉ SYNDROME

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THE clinical syndrome characterized by paralysis with sensory changes and perhaps reflected by albumino-cytologic dissociation of the spinal fluid is well defined and merits special consideration by the clinician concerned with accuracy of diagnosis. Whether the syndrome constitutes a specific disease from the standpoint of etiology remains in doubt.

In 1952 the Vanderbilt Poliomyelitis Respiratory and Rehabilitation Center was established. Since the differential diagnosis between the Landry-Guillain-Barré syndrome and poliomyelitis is frequently difficult, many patients referred to the Center as having poliomyelitis ultimately proved to be examples of the former. Accordingly, a study was undertaken with the following purposes: to review our experience with patients having Landry-Guillain-Barré syndrome; to accurately assay the recovery rate of the paralysis associated with the syndrome; and to determine whether the course of the paralysis is consistent enough to lend weight to the hypothesis that the Landry-Guillain-Barré syndrome does constitute a specific disease.

Several papers reflect a wide spectrum of opinion regarding etiology and classification. Ford[1] feels that the albumino-cytologic dissociation is not specific since patients showing such spinal fluid changes may have had diphtheritic polyneuritis or neuropathies associated with other specific illnesses. Further weight is lent to this point by papers which have described the syndrome in association with infectious mononucleosis,[2] multiple myeloma,[3] Cushing's disease,[4] and other diseases. One case of proved tuberculous meningitis originally showing spinal fluid findings typical of the Guillain-Barré syndrome has been noted in our files. Ford[1] classifies the examples of the Landry-Guillain-Barré syndrome not associated with specific diseases under the heading: acute infective polyneuritis of unknown origin.

Lewey,[5] in a critical analysis, adopted a moderate position by maintaining that although such cases are a heterogeneous group, the eponym "Guillain-Barré syndrome" is widely accepted and used and should be retained in order to best describe the various polyneuropathies.

Finally, Haymaker and Kernohan[6] after reviewing the literature completely and analyzing 50 fatal cases, clinically and pathologically, concluded that the eponym "Landry-Guillain-Barré syndrome" remains useful for those cases exhibiting primary motor radiculopathy with or

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without sensory changes. Changes in spinal fluid cell count and protein content were said to be incidental to the disorder. The pathological data included in their excellent paper certainly support the view that this may be a specific entity.

PATIENT MATERIAL

The criteria for the diagnosis of Landry-Guillain-Barré syndrome in this series are: paralysis; absence of serological and cultural evidence of poliomyelitis; absence of other specific disease; increase in spinal fluid protein content at some time during the course of the disease; and a normal number of white blood cells in the spinal fluid.

The records of all patients seen in Vanderbilt Medical Center from 1952 through August, 1958, and suspected of having Landry-Guillain-Barré syndrome were reviewed. Thirty-seven cases met the criteria outlined above. Eighteen of the patients were males, 19 were females. The youngest patient was 8 months old at the time of onset while the oldest was 72 years of age. Twenty-two patients were 15 years of age or younger. The mean age of onset was approximately 12 years.

HISTORY

Chief complaints included "weakness" or paralysis in 29 cases. Dyspnea was given as the leading symptom by 2 patients. Dysphagia and diplopia were also mentioned by 2 patients. Numbness was a primary complaint with 4 patients. Pain, meningismus, ataxia, vomiting, and convulsions were occasionally noted.

Nineteen patients had had an antecedent illness within one month of the paralytic disease. Fourteen patients had upper respiratory infections; 3, gastroenteritis; 1, pyelonephritis; and 1, a mild nonspecific febrile illness (Table I).

TABLE I

ANTECEDENT ILLNESS	NUMBER
Upper respiratory infection	14
Gastroenteritis	3
Pyelonephritis	1
Nonspecific febrile illness	1
None	18
Total	37

Seventeen patients had no pain prior to admission. Nineteen complained of pain in the extremities or back. Only 8 had headache.

Vomiting was experienced by only 9 of the 37 patients. Twelve patients had paresthesia, usually of the extremities, and 4 complained of ataxia.

PHYSICAL EXAMINATION

On physical examination signs of meningeal irritation were noted in 9 of the 37 patients. Thirty-one patients had absent or diminished tendon reflexes. Five patients had normal reflexes at the time of admission and 1 patient was thought to have hyperactive tendon reflexes. Papilledema was noted in only 1 of the 36 patients in whom funduscopic examination was described.

LABORATORY STUDIES

Examination of the spinal fluid revealed that the pressure was elevated above 150 mm. water in 14 patients. Seven patients had normal pressure determinations; 16 patients failed to have pressure measurements.

The white blood cell count of the spinal fluid ranged from 0 to 10 cells

per cubic millimeter, with one exception. This patient's spinal fluid contained 68 lymphocytes per cubic millimeter with a protein content of 364 mg. per cent.

The protein content ranged from 62 to 880 mg. per cent. When several specimens of spinal fluid were examined from the same patient, the highest value for each was used to determine the mean value for all patients which was approximately 195 mg. per cent. The spinal fluid of the patient with 62 mg. per cent of protein had no cells. This was also true of the patient whose spinal fluid contained 880 mg. per cent. The sugar content of spinal fluid was normal in 27 of 28 cases so examined. Spinal fluid culture for bacteria was done in 26 cases. Twenty-five were sterile while one was considered contaminated.

Examination of paired sera for significant rise in complement fixation titer against mumps, lymphocytic choriomeningitis, Eastern equine encephalomeylitis, Western equine encephalomyelitis, and St. Louis encephalitis was negative in the 8 patients studied. Likewise, in these same 8 patients, neutralization antibody tests and stool virus cultures showed no evidence of poliomyelitis.

HOSPITAL COURSE

Fever was absent or mild in most of these patients. Of 37 patients, 16 had no temperature reading above 100° F. Fifteen had single or infrequent elevations into the 100.2° to 101° F. range. The remaining 6 had fever above 101° F. but this was associated with complicating infections or a terminal state.

Paralysis was noted in every patient. Of the 37 patients, paralysis of the lower extremities was present in 34 patients and of the upper extremities in 30. Cranial nerves were affected in 20 patients, of whom 12 had facial nerve paralysis. Respiratory muscles were significantly involved in 12 patients; 9 required respiratory aids, initially the tank respirator in each case (Table II).

TABLE II

DISTRIBUTION OF PARALYSIS	
PARALYSIS	NUMBER
Lower extremities	34
Upper extremities	30
Cranial nerves	20
Facial nerve	12
Respiratory muscles	12
Requiring respiratory aids	9

Treatment consisted primarily of supportive care, respiratory aids when indicated, orthopedic devices, and physical therapy. The results of cortisone and/or corticotropin therapy in 5 patients and British Anti-Lewisite therapy in 3 patients were inconclusive.

TABLE III. FOLLOW-UP

PATIENTS	NUMBER
Improved	33
Dead	3
Unknown	1
Total	37

Three of the 37 patients died during the initial phase of the illness. One probably had severe pneumonitis as the immediate cause of death, but no autopsy was done. The others died as a result of vascular collapse. Pathological findings in one of these included moderate lymphocytic infiltration and scattered demyelinization of the few peripheral nerves examined. No lesions were noted in the central nervous system.

One patient (J. W., Fig. 1) experienced a relapse two months after the onset of the first attack. Prior to this relapse, he had approached complete recovery. Eventually he recovered completely from the second episode.

FOLLOW-UP

Of the 34 living patients, 4 could not be located for follow-up. Of these 4, 3 were known to be improving at the time of discharge. The record of 1 patient gave no information as to the course of the disease after the initial diagnosis was made (Table III).

Using a standard method of muscle testing and scoring,[7] it has been possible to quantitate the paralysis in many of our patients. The muscle examinations were done almost exclusively by one of us (D. F.) according to the method cited. The mass of each muscle or muscle group was quantitated and used to appropriately weigh the result obtained. The consistent reproducibility of results gives weight to the hypothesis that this can be an objective technique for the evaluation of muscle function.

Data on most of the patients permitted serial quantitation of the paralysis. The muscle examinations done on these patients were reviewed, and 27 patients could be found for re-examination. For each patient, the paralysis was quantitated and compared with time. No uniform rate of recovery could be shown by this method; in fact, several dissimilar patterns emerged as illustrated below.

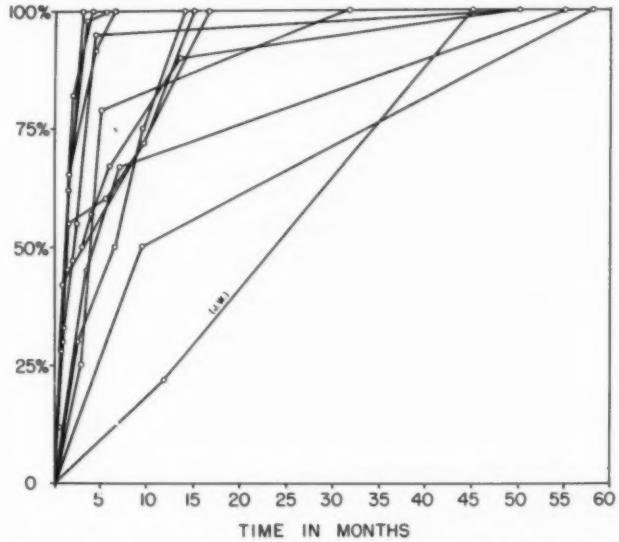

Fig. 1.—Summary of 12 patients who reached full recovery or who failed to improve further. One hundred per cent represents maximum improvement. Zero per cent represents maximum paralysis.

An adult patient illustrated in Fig. 2 had at the height of her disease approximately 87 per cent total muscular paralysis. She subsequently

regained function to the point where only 40 per cent involvement was present 13 months after the onset of her illness. Since that time we have noted little change.

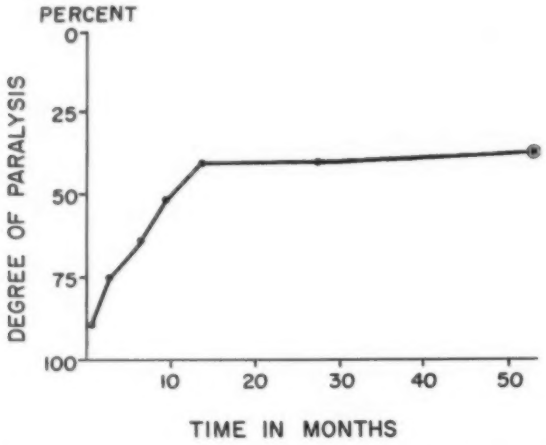

Fig. 2.—Recovery pattern of a severely involved patient with significant residual paralysis.

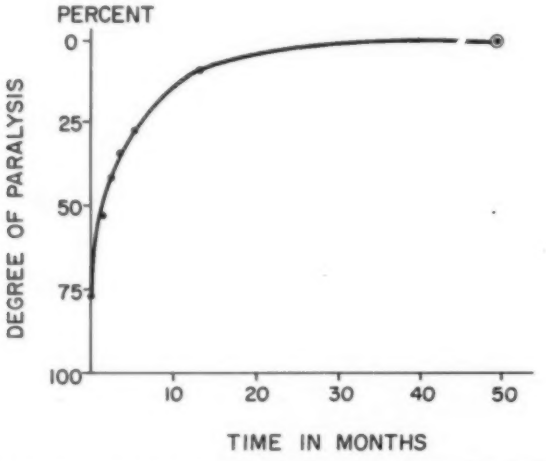

Fig. 3.—Recovery pattern of a severely involved patient with complete recovery.

The recovery rate of another severely involved patient (76 per cent paralyzed) is depicted in Fig. 3. This patient completely recovered. It is noteworthy that this is considerably more recovery than a patient with comparable poliomyelitis would exhibit.

Another recovery pattern is illustrated in Fig. 4. This patient, although less severely involved (57 per cent) than the other 2 cases cited, did not fully recover.

Of the 27 patients with one or more recorded muscle examinations, only

16 could be followed closely enough to provide information as to final outcome. Patients were finally examined 2 to 7 years following their original illness. Eight patients recovered to within 7 per cent of normal. Table IV lists the 8 patients who fully recovered. The figure under the maximum initial paralysis column represents the most severe degree of paralysis recorded during the disease. The maximum permanent paralysis column represents the degree of final residual paralysis, and the length of follow-up is noted in the last column. No patient had residual functional disability. It is significant that there was no apparent correlation between the initial and final degree of paralysis.

Of the 16 patients who had recovered completely or who had experienced no improvement for 6 months or more, only 12 had had an early enough initial examination to make the following analysis possible.

In Fig. 1, maximum initial paralysis was assigned a value of 0, while maximum recovery was assigned a value of 100. Intermediate points were appropriately interpolated, such points being compared with duration of illness in months. It should be noted that in many cases because of long intervals between the last two muscle examinations we do not know exactly where in time the last point should fall.

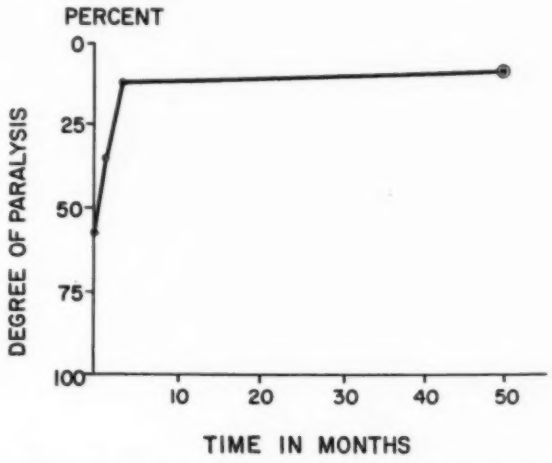

Fig. 4.—Recovery pattern of a patient with moderate initial paralysis who had a significant residual paralysis.

TABLE IV. RESIDUAL PARALYSIS AMONG EIGHT FUNCTIONALLY NORMAL PATIENTS

NAME	MAXIMUM INITIAL PARALYSIS (PER CENT)	MAXIMUM PERMANENT PARALYSIS (PER CENT)	FOLLOW-UP (YEARS)
W. D. K.	76	2	4½
R. G. J.	41	6	3
W. H. S.	35	3	2
J. M. W.	45	0	3½
M. R. W.	58	3	5
R. W.	*	1	4
L. W.	47	3	1½
R. B.	*	7	7

*Data not available.

It is possible to estimate that most patients (10 of 11) had 50 per cent

of their final recovery by 6 months and that recovery was probably complete by 12 months. This pattern is not unlike poliomyelitis. The obvious exception to this pattern is the patient (J. W.) who relapsed.

CONCLUSIONS

It is concluded that: The Landry-Guillain-Barré syndrome remains a useful clinical category. Usually 50 per cent or more of the eventual recovery of muscle power occurs during the first 6 months of convalescence.

SUMMARY

A brief outline of several perspectives of the Landry-Guillain-Barré syndrome has been given, and clinical findings in 37 cases were reviewed according to fairly rigid diagnostic criteria. The recovery rate pertaining to the paralysis in 16 patients was analyzed.

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PATTERNS OF INFECTION WITH ENTEROVIRUSES

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FOLLOWING the widespread application of tissue culture techniques to studies of poliomyelitis,[1-3] it soon became obvious that many patients who had illnesses hitherto described as "nonparalytic poliomyelitis" were infected with either Coxsackie or enteric cytopathogenic human orphan (Echo) viruses and not with poliovirus. At present, over 40 distinct antigenic types of enterovirus,[4] which includes the poliomyelitis, Coxsackie, and Echo groups of viruses, have been described. However, relatively few serologic types of enterovirus have been isolated regularly from patients during epidemics of aseptic meningitis or other illness. Since in areas such as Charleston and West Virginia[5] a wide range of enterovirus types may be isolated from stools of healthy residents, especially during the summer months, it is of paramount importance to obtain additional evidence that a particular virus which was isolated from the feces of a patient caused an infection at the time of his illness. This evidence is obtained by isolation of the same antigenic type of virus from a site remote from the alimentary tract, such as the cerebrospinal fluid, or by serologic means in which an attempt is made to demonstrate a rising titer of neutralizing antibody against the patient's own virus or the prototype virus of the same antigenic type. Monkey kidney cultures occasionally harbor viruses before material from patients is inoculated. In order to eliminate the latter possibility, it is necessary to demonstrate a rising titer of antibody against this new agent in paired sera from the patient who donated this virus, or at least to detect antibody in that patient's serum.[6]

Since 1955 two striking features have been observed during epidemic spread of enteroviruses, especially in Canada and the northern part of the United States. (1) One antigenic type of virus is predominant during a particular season but a completely different antigenic type becomes dominant one or two seasons later. (2) The symptomatology produced following infection with an enterovirus may vary from an uncomplicated aseptic meningitis,[7, 8] pleurodynia,[9-11] an exanthem which occurred either alone[12, 13] or was accompanied in some instances by aseptic meningitis,[8, 14-16] or pharyngeal lesions,[17] to benign pericarditis[9, 18] in children and adults or fatal myocarditis[19-21] in newborn infants.

The uniform picture of aseptic meningitis as the only clinical manifestation of infection with Coxsackie B5 virus in Minnesota[7] and Iowa[22] in 1956 is in sharp contrast to the wide spectrum of syndromes observed in 1958. In Minnesota 61 out of 113 persons who had aseptic meningitis excreted Coxsackie B5 virus in the feces and

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one excreted Coxsackie B3 virus. Rising titers of Coxsackie B5 antibody in paired sera from 9 patients together with elevated titers in serum pairs from a further 12 patients, all of whom shed Coxsackie B5 virus in the stools, confirmed that this virus infected these patients at the time of illness. Although Coxsackie B5 virus was not isolated from cerebrospinal fluids of 13 Minnesota patients with aseptic meningitis, it was isolated from 2 out of 16 fluids obtained from Iowa patients.

In Minnesota during 1957 the dominant enterovirus was Echo 9.[15] This was the only serotype isolated from feces of 15 of 22 patients who had aseptic meningitis with or without an exanthem, and rising Echo 9 antibody titers were demonstrated in paired sera from 21 patients. No Coxsackie B5 infections were reported during 1957.

In Marshalltown, Iowa, during 1955 Echo 4 virus was recovered from 21 of 46 persons who had aseptic meningitis and from 2 of 11 healthy family contacts.[23] Rising Echo 4 antibody titers in paired sera from 12 of 21 patients with aseptic meningitis or minor illness and 2 of 4 family contacts were consistent with infection by Echo 4 virus. However, in Iowa during 1956 Coxsackie B5 was virtually the only serotype of virus recovered from patients with aseptic meningitis.[22]

In western New York State,[24] Connecticut,[25] and Massachusetts[26] infections with Echo 6 virus were manifest clinically almost exclusively as aseptic meningitis. However, Karzon[27] has shown that during a single epidemic of this syndrome in 1955 strains of Echo 6 virus may show considerable antigenic variation. Some strains had high specificity requiring between 20 and 100 times higher concentrations of antibody to be neutralized by prototypical antiserum than those of lower specificity such as the prototype D'Amori strain.

In Massachusetts during 1951 viruses antigenically similar to Echo 16 (Harrington strain) were isolated from the feces of 7 patients who had aseptic meningitis.[26] During this same year, cytopathogenic agents were isolated from feces of patients in Massachusetts who were afflicted by an unusual epidemic exanthem, termed the "Boston exanthem."[12] None of these patients exhibited signs of aseptic meningitis, yet viruses isolated from them were similar antigenically to Echo 16 virus. Viruses antigenically related to those isolated from patients with the Boston exanthem were recovered from patients during a small outbreak of the same disease in Pittsburgh during 1954.[13]

Further evidence for an etiologic relationship between an enterovirus and an exanthem which occurred either alone or in combination with aseptic meningitis was obtained in England,[8, 16] Belgium,[28] and Toronto[14] during the late summer of 1956 when Echo 9 virus which was pathogenic for newborn mice was isolated regularly from feces and less frequently from cerebrospinal fluids of patients exhibiting these syndromes. At a Royal Air Force Station near Huntington we studied 6 patients, belonging to 3 families, who had a transient morbilliform rash, fever, and headache, but no patient had neck stiffness. Echo 9 virus was isolated from feces of 3 patients and rising antibody titers against the Bourn strain of Echo 9 virus[8] in

paired sera from 4 patients showed that they were infected with this virus at the time of illness. During the autumn of 1955, when 11 cases of aseptic meningitis due to Echo 9 virus were hospitalized in Cambridge,[29] Echo 9 virus was isolated from cerebrospinal fluids, feces, and throat washings of patients living in East Suffolk who developed aseptic meningitis which was complicated by a rubelliform rash in about 25 per cent of the cases.[30]

At The Hospital for Sick Children, Toronto, between 1950 and 1955, of the 96 cases of aseptic meningitis studied,[31] 18 were infected with Coxsackie B viruses, principally types B2 and B4. Occasional Echo viruses were isolated from aseptic meningitis cases in 1952 and 1954, but during 1955, 15 enteroviruses were isolated from 27 patients with aseptic meningitis,[32] of which 12 were untyped Echo viruses and one was a strain of Echo 9 (Table I). However, by 1956 Echo 9 virus was the sole serotype present in 58 isolations from stools of 94 patients and in 15 isolations from cerebrospinal fluids of 48 patients who had aseptic meningitis alone or accompanied by a rubelliform rash.[14] In 1957 34 virus isolations were made from stools of 51 patients with aseptic meningitis whether or not the aseptic meningitis was accompanied by a rash, and again Echo 9 was the predominant immunotype identified (Clarke and associates, unpublished).

In 1958, between June 4 and December 31, we investigated 69 cases of aseptic meningitis, 18 cases of pleurodynia, 11 cases of acute abdominal pain, 8 cases of pericarditis, and 6 cases of paralytic poliomyelitis. No cases of an exanthem accompanying aseptic meningitis were encountered.

The symptomatology of the aseptic meningitis was typical, with sudden onset of headache, fever, vomiting, stiff neck, and pleocytosis of the cerebrospinal fluid. Fecal samples were obtained from all 69 patients between 1 and 8 days after onset, and Coxsackie B5 virus was isolated from 33 patients, Echo 9 virus from 5 patients, and Coxsackie A9, B3, B4, Echo 6, and an untyped enterovirus were isolated singly from another 5 patients (Table II). Cerebrospinal fluids were obtained from 46 patients, and Coxsackie B5 virus was isolated from 17 fluids, Echo 9 virus from 4 fluids, and Coxsackie B4 virus from one fluid. Fivefold or greater increases in Coxsackie B5 neutralizing antibody titer which were obtained in paired sera from 12 patients and elevated antibody levels which were detected in early and late sera from another 16 patients (all 28 patients excreted Coxsackie B5 virus in feces or cerebrospinal fluid) showed that these patients were infected with this virus at

TABLE I. ENTEROVIRUSES ISOLATED IN TORONTO BETWEEN 1955 AND 1958

YEAR	NUMBER TESTED	NUMBER POSITIVE	PREDOMINANT VIRUS	OTHER VIRUSES
1955	27	15	Echo (untyped)	Coxsackie B2, Echo 9
1956	94	58	Echo 9	
1957	51	34	Echo 9	Coxsackie A9, B3, B5
1958	69	43	Coxsackie B5	Coxsackie A9, B3, B4, Echo 6, 9

the time of illness. A rising titer of Echo 9 antibody was found in paired sera of one patient who excreted this virus; 7 other serum pairs had elevated antibody levels in early and late sera. The single Coxsackie B3 virus excretor had elevated antibody levels against this virus in both serum samples.

We investigated 18 patients with pleurodynia whose symptoms developed between August 1 and October 21, 1958. The onset was sudden, with fever, weakness, and a sharp pain in the chest on deep inspiration. A loud pleural friction rub was heard in 9 patients and this persisted for 1 week or less. No evidence of associated pneumonitis and no pleural effusion was detected in chest x-ray but usually the lungs appeared incompletely expanded since the patients did not take full breaths due to the pleuritic pain. Headache and neck stiffness occurred in 6 patients before or after onset of pleurodynia, and lumbar puncture of 5 patients revealed cerebrospinal fluid cell counts of more than 50 cells per cubic millimeter in 4 patients.

Coxsackie B5 virus was isolated from feces collected from 16 of 18 pleurodynia patients between 1 and 15 days after onset and from cerebrospinal fluids obtained 3 and 10 days after onset from 2 of 5 patients who had aseptic meningitis in addition to pleurodynia. Rising titers of Coxsackie B5 neutralizing antibody were detected in paired sera from 9 patients, a further 8 patients had elevated antibody titers in both early and late sera, and a high antibody titer was detected in a convalescent serum from one patient.

In 11 children who became ill between August 7 and November 15, the chief presenting symptom was acute abdominal pain either in the epigastrium or iliac fossae, usually accompanied by vomiting and fever. Isolation of Coxsackie B5 virus from the feces of 5 patients together with elevated or rising titers of Coxsackie B5 antibody in paired sera of 3 patients confirmed that symptomatic infection by this virus may occasionally be manifest by an attack of abdominal pain.

Between July 17 and October 11, we studied in detail 8 children between 4 and 12 years of age who suffered from acute benign pericarditis. Three children developed fever and sore throats which did not remit after several days' chemotherapy at home, and

TABLE II. VIRUS ISOLATIONS AND ANTIBODY STUDIES ON ASEPTIC MENINGITIS IN TORONTO, 1958

INFECTING VIRUS	VIRUS ISOLATIONS		ANTIBODY TITERS IN PAIRED SERA		
	FECES	CEREBROSPINAL FLUID	RISING	ELEVATED	NEGATIVE
Coxsackie B5	33	17	12	16	19
Echo 9	5	4	1	7	11
Coxsackie A9	1	--	--	--	--
Coxsackie B3	1	--	--	1	--
Coxsackie B4	1	1	--	--	--
Echo 6	1	--	--	--	--
Untyped	1	--	--	--	--
Specimens positive	43	22	--	--	--
Specimens tested	69	46	--	--	--

subsequent examination revealed a pericardial friction rub. In four children who presented fever and chest pain of sudden onset, pericardial rubs were heard when first examined. Cardiac enlargement was absent or minimal. Pericardial effusion was detected in one patient, and 50 ml. of serosanguineous fluid was removed. Flattening and inversion of T waves principally in Leads V_3 to V_5, characteristic of nonspecific pericarditis, were detected in electrocardiograms of 6 patients. All patients made complete recoveries 3 to 6 weeks after onset of symptoms.

Coxsackie B5 virus was isolated from fecal samples obtained from 5 of 8 patients between 6 and 23 days after onset. Elevated titers of Coxsackie B5 neutralizing antibody were detected in paired sera from all 8 patients. Owing to the lateness of collection of acute phase sera in most cases and the rapid increase in antibody titer shortly after onset of symptoms following Coxsackie B5 infection, it was not possible to detect significant increases in titer in paired blood samples. Since Coxsackie B5 virus was not epidemic in Toronto before 1958, the height of the antibody response in these children is consistent with recent infection by this virus. Also, the presence of Coxsackie B5 virus in the feces of 5 patients at the time of illness strongly suggests an etiologic relationship between Coxsackie B5 virus and pericarditis.

Although a particular serotype of enterovirus has been encountered repeatedly in association with a single syndrome such as aseptic meningitis or this syndrome in combination with pleurodynia or rash in some epidemics, experience in Toronto during 1958 has shown that a wide spectrum of syndromes may be produced following infection with one serotype, Coxsackie B5 virus, and this spectrum may include pericarditis.

SUMMARY

The wide diversity of clinical syndromes, including pericarditis, which were encountered following infection with Coxsackie B5 virus in southern Ontario in 1958 is in sharp contrast to the uniform clinical picture of aseptic meningitis which resulted from infection with this virus in Minnesota and Iowa during 1956.

Clinical manifestations of infection by Echo 9 and Echo 16 viruses may appear either as an exanthem or as aseptic meningitis or, in the case of Echo 9 virus, both conditions may occur in the same patient.

The abrupt changes in antigenic types of predominant enteroviruses during successive seasons as observed in southern Ontario and in some areas of the northern United States has been discussed.

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Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, *Editor*
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THIS 1-month-old girl entered this hospital because of a ravenous appetite, frequent stools, a rapid pulse, and jaundice. Fifteen months before her admission her mother developed clinical hyperthyroidism. The mother was treated with radioactive iodine and, subsequently, propylthiouracil. The latter drug was discontinued during the second month of pregnancy. At the 7½ month of pregnancy, her membranes ruptured and, because of a previous cesarean, a repeat section was performed. The infant, who weighed 3 pounds, 3 ounces, breathed and cried promptly. At this time the heart rate was 200 per minute, the thyroid was enlarged, and the liver and spleen greatly so. Oxygen therapy was given and after 5 hours the heart rate dropped to 120 and the liver and spleen receded. Jaundice appeared on the fifth day of life. On the tenth day of life brief cyanotic spells were noted, accompanied by an increase in the size of the liver and in the heart rate. Soon thereafter she was noted to have a ravenous appetite, hyperactivity, a poor weight gain, frequent pale yellow stools, and exophthalmos. Jaundice continued, the total bilirubin level remained about 10 mg. per cent. Digoxin therapy was given for one week. After this was stopped the pulse rose from 160 to 200 per minute and the liver increased in size. Two days later she was transferred to The Children's Medical Center.

At the time of admission the vital signs were: temperature 98.5° F. (rectal), blood pressure 150 mm. Hg systolic (auscultation), pulse 169, and respirations 68 per minute. The height was 14 cm., head circumference 30, chest 28, abdomen 31, and the weight was 4 pounds, 8 ounces. The infant was very active and well hydrated but had little subcutaneous fat and a green icteric tinge. Periorbital edema was present; the eyes did not close completely during sleep. The thyroid gland was twice the usual size. The lungs were clear. The heart was very active but was not enlarged and no murmurs were detected. The peripheral pulses were bounding. The sharp liver edge was felt 7.0 cm. and the spleen 2 to 3 cm. below the costal margin. The abdomen was mildly distended but no other masses were felt. Generally the deep reflexes were hyperactive.

The initial hemogram was: hemoglobin 12.5 Gm. per cent and leukocytes 29.0 thousand per cubic millimeter. The differential smear count was polymorphonuclear cells 39 per cent, band forms 23, lymphocytes 37, and basophilic leukocytes 1 per cent. Platelets were described as normal and there

were 8 nucleated erythroid cells per 100 leukocytes. The urine contained bile, 3 plus albumin, and granular casts, but no bacteria on culture. The spinal fluid was xanthochromic, with protein 58.8 and sugar 57 mg. per cent, 128 erythrocytes, and 2 monocytes per cubic millimeter. A spinal fluid culture was negative.

The serum contained 6.9 mg. per cent direct and 12.5 mg. per cent total bilirubin, calcium 8.9, cholesterol 366, and nonprotein nitrogen 66 mg. per cent. The chloride was 111 mEq. per liter, the sodium 135 mEq. per liter, and the potassium 5.95 mEq. per liter. The protein-bound iodine was 11.6 mcg per cent and the total iodine 12.6 mcg. per cent, while the red cell triiodothyronine uptake was 27.2 per cent. The electrocardiogram was interpreted as showing sinus rhythm with sinus pauses and right and left ventricular hypertrophy. Roentgen studies revealed normal heart and lungs, with moderate hepatic enlargement.

On the night of admission the patient was anorexic and appeared in distress. By the next morning she had a weight gain of 2½ ounces, nasal congestion, and respiratory distress with intercostal retraction. She was given Digoxin, nose drops, chloramphenicol, and oxygen but showed no improvement over the next day; phenobarbital 4 mg., potassium iodide 10 mg., and propylthiouracil 25.0 mg. each 8 hours were also administered. Feedings were given by gavage. On the third hospital day, lethargy became marked; her abdomen was distended and hard, and bowel sounds were absent. She passed no gas or stools and lay in an opisthotonic position. Abdominal films now showed hepatosplenomegaly, fluid distention of the stomach, little air in the intestine, and suggestive evidence of peritoneal effusion. A barium enema did not reveal any abnormality. She received 40 ml. of whole blood, intravenous potassium iodide, antibiotics, fluids, and intramuscular Digoxin. No improvement occurred and she died early on the fourth hospital day.

DR. JAMES E. DRORBAUGH.*—The first three of the admitting symptoms, namely, frequent stools, ravenous appetite, and rapid pulse, individually in a newborn or premature infant are not in themselves alarming, but might simply indicate a hungry active infant who is treatable by increasing feedings.

The mother was treated with radioactive iodine and then propylthiouracil. Radioactive iodine therapy has never been recommended for children because, with their long-life expectancy, malignancy may develop following a long latent period. Radioactive iodine might conceivably cross the placenta and injure the infant's thyroid, producing hypothyroidism, but since this patient was thyrotoxic, this appears untenable. The administration of propylthiouracil might conceivably depress thyroid function of the infant, but again the symptoms are not compatible with this diagnosis. Propylthiouracil is also known to depress liver function, but the drug was discontinued in the second month of pregnancy, and therefore this cannot explain jaundice in the newborn period.

A heart rate of 200 immediately after birth would again, of itself, not be abnormal, but the greatly enlarged

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thyroid, spleen, and liver are definitely abnormal findings. Since the heart rate decreased to 120 per minute after 5 hours of oxygen therapy, this might suggest that the enlarged thyroid had produced obstruction of the airway, which can happen, the anoxic symptoms were then relieved by oxygen therapy. However, there is no good history of symptoms related to obstruction of the airway.

The reported failure to gain weight by 10 days of age would not be significant in a premature infant weighing 3 pounds, 13 ounces at birth since the smaller the infant at birth, the longer he takes to regain his birth weight.

The systolic blood pressure in full-term quiet infants in the first few days of life would be expected to be in the range of about 60 mm. Hg, with a slow elevation to 70 to 80 mm. Hg. within the first two months of postnatal life, so that the blood pressure of 150/0 is distinctly elevated.

The recorded weight gain at 1 month of age is below the mean expected level of 5 pounds by Bellevue standards, but not alarmingly so.

May I see the x-rays?

DR. MARTIN H. WITTENBORG.—Films on the day of admission showed the heart to be within normal limits and there were no definite signs of cardiac failure as judged by the lungs. The liver and spleen were definitely enlarged. There was moderate distention of the flanks of the protuberant abdomen, which can't be accounted for entirely by the gas pattern in the bowel. A day or two later she became more distended, but we saw no distention of the bowel to account for this; we suggested the possibility that there was free fluid in the peritoneal cavity. However, in view of this distention a barium enema was requested to rule out volvulus on the basis of malrotation. The enema confirmed the fact that the colon was normal in position and not distended in proportion to the abdomen. The film taken just two days before death showed considerable retention of the barium, very little gaseous distention of the bowel, and progressive enlargement of the abdomen, all of which would support a diagnosis of an accumulation of fluid in the abdomen.

DR. DRORBAUGH.—At the Lying-in Hospital the diagnosis in 60 per cent of our premature infants who die in the neonatal period is hyaline membrane syndrome. Another 20 per cent have some form of infection and the remaining 20 per cent are congenital anomalies or unusual and rare diseases. At this age the two most likely possibilities, I think, would be congenital anomaly or infection. In this patient there is reason to suspect the aptness of both diagnoses.

Yesterday, I luckily was looking through the Year Book of Pediatrics and in the Endocrinology Section there were two cases described which seem to fit this patient's picture very well.[1, 2] These two patients had thyrotoxicosis with hepatosplenomegaly and jaundice; both patients were from exophthalmic mothers. One patient weighed 3 pounds, 15 ounces, had symptoms very similar to those of our patient, and died at 1 month of age of bronchopneumonia.

This patient, I believe, on the basis of a history of maternal thyroid disease, a failure to gain, hyperactivity, exophthalmos, rapid heart rate, wide pulse pressures, signs of congestive

failure responding to digitalis, and the abnormal total protein-bound iodine and red cell triiodothyroxine uptake studies, had hyperthyroidism.

The patient also had a severe liver disorder, as evidenced by the liver enlargement, the high direct and indirect serum bilirubin values, and bile in the urine. I think I would consider three main possibilities for these findings: first, so-called neonatal hepatitis in which the onset of jaundice can be very early in the neonatal period and which would give this type of partition of the total bilirubin; second, the inspissated bile syndrome related to erythroblastosis, but there is no evidence for erythroblastosis here; third, biliary atresia, but this does not seem to be a likely with jaundice so early in life. However, on the basis of the report referred to above, I must conclude that the liver disease is related to the hyperthyroidism. The patient became very lethargic and opisthotonic and may have died in liver coma, and, although we have no data on the terminal bilirubin levels, liver failure is certainly related to his death. On the basis of the roentgen interpretation and abdominal distention, I predict that ascites and splenomegaly, secondary to portal hypertension, will be found. I do not believe she had bronchopneumonia.

DR. CRAIG.—We are happy to have Dr. Milton Hamolsky of the Department of Medicine of the Beth Israel Hospital here today. Dr. Hamolsky did some interesting studies on this infant.

DR. MILTON HAMOLSKY.—First, we are very chary about the use of I^{131} in young women and, indeed, arbitrarily have set a lower limit of 40 years of age in our clinic for the use of such therapy. This patient received I^{131} 3 months before the estimated onset of gestation. The evidence is quite clear that the thyroid of the fetus does not take up I^{131} until about 3 months after conception, so we have a 6-month period between the time of I^{131} administration and the period of the fetus' ability to take up iodine. I think I would tend to rule out I^{131} as participating in any way in this infant's subsequent course. Even in adults at the end of two months a therapeutic dose of I^{131} (for hyperthyroidism) is virtually out of the body. There are some 13 recorded cases of women who were given I^{131} for therapeutic purposes while known to be pregnant, mostly under critical conditions. All of their offspring were perfectly normal and have continued to be, in the follow-up studies. There is, to date, no evidence of an effect on subsequent offspring of prior administration of I^{131} for thyrotoxicosis.

In the course of some experimental studies of tissue uptake of thyroid hormone, we found that if one adds, in vitro, a small labeled dose of thyroxin or triiodothyronine to the whole blood of a patient, incubates the blood for a couple of hours, and then counts the proportion of labeled material which has accumulated on the red cell membrane, and if it is not washed off in 5 saline washings, this correlates surprisingly well with the clinical status of the patient. We have done some 2,500 tests now, and we find that in a normal subject about 11 to 17 per cent (expressed per 100 hematocrit) of the radioactively labeled I^{131} triiodothyronine adheres to the red cell after 2 hours' incubation. Cases of hyperthyroidism average 23 per cent (17 to 36),

while all our myxedema patients have had levels below 11 per cent. We are carrying out estimations on a large series of cretins before and during therapy, through the courtesy of Dr. Crigler of this hospital.

The involvement of the thyroid gland in pregnancy has been known for a long time. The ancients first pointed out that the thyroid gland in most females increased three or four times in size during pregnancy. Abnormalities of thyroid function, hyperthyroidism, or hypothyroidism are known to be associated with a high incidence of premature deliveries, congenital abnormalities, or intrauterine deaths. It was soon found, when oxygen uptake studies were done, that there was a high oxygen consumption in pregnancy and it was assumed that there was an element of hyperthyroidism present. However, most authors have been satisfied by the more than adequate explanation that the elevated oxygen consumption in pregnancy is due to the growing fetus and the increased cardiac output, arteriovenous intrauterine shunts, and increased peripheral blood flow. The matter rested there until protein-bound iodine tests became available. Then it was shown that the protein-bound iodine becomes elevated in about the third month of pregnancy. Indeed, in a large series of patients suffering from chronic miscarriages, a failure of elevation of the protein-bound iodine presaged miscarriages. Groups in South America, Italy, and France studied radioactive iodine uptakes in pregnant women and found a striking increase in I^{131} uptake and turnover by the thyroid gland. We then came back to the idea that there is evidence of hyperactivity in the thyroid gland and the possibility of some of the symptoms in pregnancy being due to a hyperthyroid component.

It was found, by several workers, that a specific protein fraction thyroxin-binding globulin was strikingly increased in early pregnancy. It was also found that this increase could be induced by the administration of estrogens; therefore, the concept arose that in pregnancy, with its accompanying the increased amount of estrogen, there was an increased production of thyroxin-binding protein which was then able to take up more thyroxin. The amount of thyroxin (plus triiodothyroxine) bound to this specific protein is what is being measured when protein-bound iodine is measured. Our studies are an attempt to find out how protein-bound iodine gets into the tissue by measuring, as previously mentioned, the triiodothyronine uptake by the erythrocyte membrane. When we turned our studies to pregnant women, we found that the pregnant patient with the high protein-bound iodine had a very low red blood cell uptake. If one is interested in thinking teleologically, then one says that when the thyroid gland becomes active in pregnancy the body also makes a larger pool for hormones by providing a "sponge" to hold on to this hormone so that the entire body is not flooded by it. This protects the pregnant woman from thyrotoxicosis. Indeed, the present concept is that pregnancy ameliorates pre-existing thyrotoxicosis.

Now this patient demonstrates the story very well. Since she was treated with propylthiouracil, she was obviously still hyperthyroid when she became pregnant. She became pregnant

but because she felt so well and because her doctor thought she should not take medicine during pregnancy, the propylthiouracil was discontinued. She went through her pregnancy without symptoms and with no palpitation or excessive sweating. Within three weeks of delivery of the infant, her symptoms returned, and by the time we first saw her, she was again grossly thyrotoxic.

Furthermore, we have had some 6 patients, pregnant for 3 to 5 months, whose red cell uptake remained perfectly normal instead of decreasing; each of the 6 have subsequently had miscarriages. Such cases have also failed to show an elevation of protein-bound iodine. Therefore, it seems that in pregnancy there must be an increased amount of binding protein which may serve to prevent excess thyroxin from getting into the tissue and that if this increase is lacking, there is a high incidence of miscarriage.

Another disease state which will alter this binding capacity is nephrosis; the nephrotic patient has a low basal metabolic rate and low serum protein-bound iodine as evidence of hypothyroidism. Most such patients have failed to respond to thyroid therapy, and various I^{131} studies have been normal. The concept now is that in addition to other protein deficiencies the nephrotic lacks the ability to make or maintain an adequate amount of thyroxin-binding protein, but there is plenty of thyroxin. In our red cell uptake studies the tissues actually incorporate more labeled hormone than normal. Finally, of pertinence in this case is the fact that in hepatitis or in severe liver disease we have found a decreased production of this binding protein.

Therefore, it seems conceivable that although the mother's thyroxin-binding protein was increased, which increase is usually found to be reflected in the cord blood, the liver damage in this case may have interfered with the synthesis of this protein so that the infant did not have adequate binding capacity to handle the increased maternal thyroxin levels (or its own) and thus the tissues were subjected to an excess of thyroid hormone, resulting in thyrotoxicosis.

If I may add a word about therapy, I would begin by a brief note of thanks that I was not responsible for the therapy in this very difficult case!

The use of iodide (including parenteral use), propylthiouracil, and the various supportive measures were certainly clearly indicated in our present state of knowledge. The only suggestions I can offer, retrospectively, would be consideration of the use of (1) a corticosteroid in this critically ill child, despite the appreciable risk of spreading infection (cortisone has been reported to be effective in cases of "thyroid storm," and there is some evidence, albeit confusing, of an antithyroid effect), and (2) of one of the reserpine compounds which appear to have a striking ameliorative effect on certain aspects of hyperthyroid symptomatology, although the basic hypermetabolic disturbance is not reversed.

Of pertinence here also is therapy of the mother during gestation. In former days, thyrotoxicosis was considered an indication for therapeutic abortion, but available therapy now makes it possible to permit continuation of the pregnancy. Mild cases have been treated with stable iodide alone or stable iodide followed by subtotal thyroidectomy.

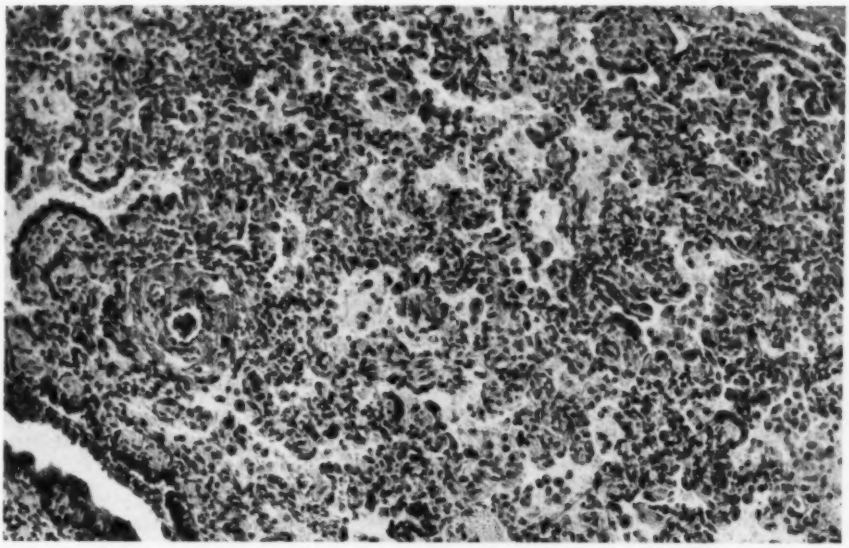

Fig. 1.—Photomicrograph of the lung. The lung shows chronic aspiration and interstitial pneumonia and edema. (Hematoxylin and eosin ×170.)

Fig. 2.—The large irregular thyroid has greatly distended vessels. It is separate from the thyroid cartilage.

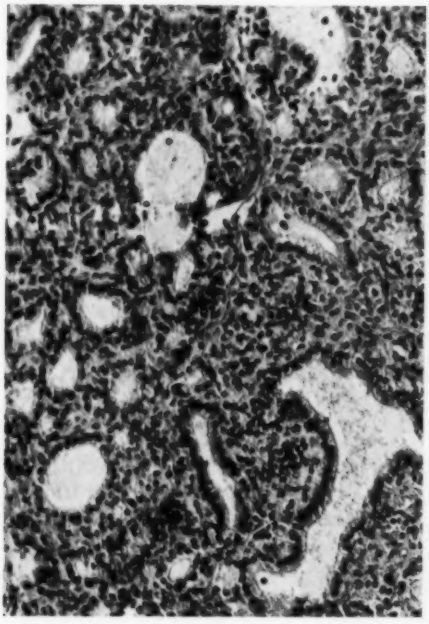

Fig. 3.—Photomicrograph of the thyroid. The follicles are irregular in size, lined with a high columnar epithelium, and have a scant pale colloid. (Hematoxylin and eosin ×310.)

Most recently, the concensus of opinion favors the use of propylthiouracil, which has been very effective in maintaining normal pregnancy and permitting normal offspring. An unusual complication is the occurrence of a goiter in the child, occasionally large enough to cause respiratory distress; usually, however, the goiter promptly disappears following delivery. It is considered important in the adequate treatment of hyperthyroidism to avoid production of the hypothyroid state by overvigorous therapy. This, in turn, has been managed quite well by the seeming paradox of administering 1 to 2 Gm. of desiccated thyroid daily in addition to the propylthiouracil. As indicated above, as pregnancy continues, the hyperthyroidism may lessen, so that close and careful observation is necessary.

DR. CRAIG.—Thank you very much, Dr. Hamolsky.

The thyroid gland was twice the normal size with a tremendous increase in the size of the isthmus (Fig. 1). Histologically there was good evidence of overactivity of the thyroid tissue, with high columnar lining epithelium having a tendency to papillary infolding and many acini containing little colloid while others had none (Fig. 2). The heart appeared to be large by gross inspection, though by weight it was barely over the normal standard. The heart, microscopically, displayed slight endocardial thickening, slight myocardial hypertrophy and fibrosis. The lungs were diffusely atelectatic and there was a bronchopneumonia of an aspiration type; this has been an important cause of death in other infants with hyperthyroidism who have been gavage fed. The liver was green, smooth, and enlarged two and a half times. The liver sections were typical of the changes seen in "neonatal" hepatitis, with marked distortion of the liver cell cords, the formation of many syncytial giant cells, extramedullary erythropoiesis, an inflammatory response in the portal triads, and little diffuse fibrosis. These changes cannot be interpreted as evidence of cirrhosis. Bile stasis was noted in the bile canaliculi, liver cells, and von Kupffer cells, but not in the bile ducts; the hepatic ducts were grossly patent. Scattered necrobiotic liver cells were present in the parenchyma. There was no significant accumulation of fluid in the intestine, but the intestines were moderately distended with fecal material, and this may have accounted for the diffuse ground-glass appearance in the roentgenogram.

We believe that this infant had hyperthyroidism with enlargement of his heart, bronchopneumonia, and what is known (for want of a precise term) as "neonatal hepatitis." The etiology of the latter is unclear. There have been several suggestions: first, that it represents serum hepatitis transmitted from the mother, though, aside from a single successful passage of an icteric agent to volunteers,[4] attempts at passage of an agent have been unsuccessful[5]; second, that it represents a congenital malformation at the level of the bile canaliculi,[6] or that it is an hereditary disorder of unusual nature.[7] None of these assumptions are on undebatable grounds.

The effect of the placental barrier to maternal influences on the fetal thyroid as proposed in an editorial in the British Medical Journal[8] I cite with some diffidence because all the

ideas are in a rapidly developing field. They contend that normal thyroid-stimulating hormone does not get across the placenta; Dr. Hamolsky has expressed himself on this point. Mothers with treated hyperthyroidism and increasing persistent exophthalmos have had infants with exophthalmos but without hyperthyroidism. Iodine, as determined by radioactive iodine, crosses the placenta promptly and is then taken up by the fetal thyroid, as Dr. Hamolsky mentioned, by the end of the second month. Thyroid hormone apparently goes across very slowly and inadequately since an infant of a mother with normal thyroid activity may be a cretin at birth. Thyroxin goes across the placenta slowly since it requires some 69 hours to reach an equilibrium between the mother's and the fetus' serum levels. Propylthiouracil also will pass across the placenta and may affect the infant's thyroid and may produce an increase in thyroid-stimulating activity which may, after birth, cause a rebound in the infant's thyroid activity and may produce an increase in thyroid-stimulating activity which in turn, may cause a rebound resulting in hyperthyroidism.

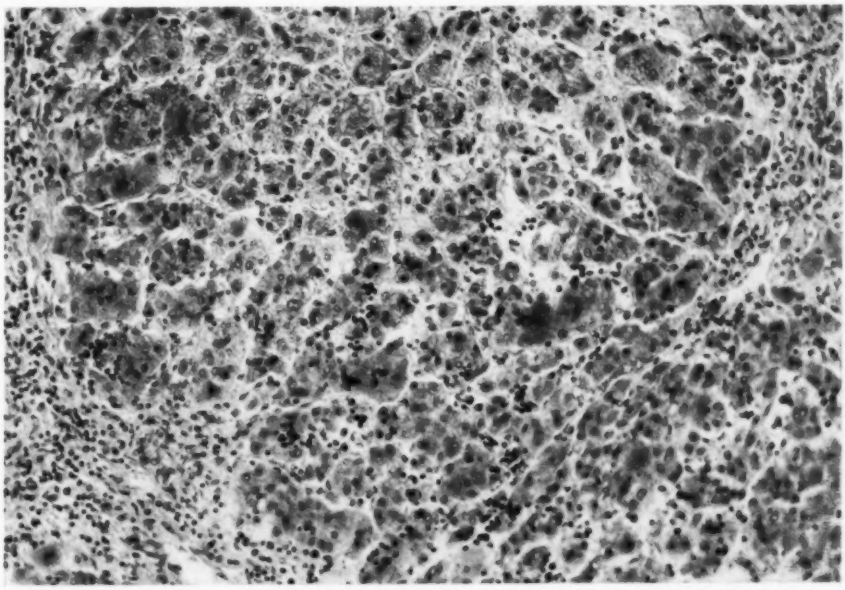

Fig. 4.—Photomicrograph of the liver. Marked distortion of the liver cell plates, giant cell formation, inflammation, and extramedullary erythropoiesis are features seen in the liver section. (Hematoxylin and eosin ×200.)

Dr. Hamolsky, would you care to say a word on this?

Dr. Hamolsky.—Up until 10 years ago everything was understandable, thyroid wise, in terms of thyroxin. Too much thyroxin was thyrotoxicosis, and not enough was myxedema. Now we are wrestling with some 26 or 28 analogues of triiodothyronine, all of which

are doing things more strongly and more quickly than thyroxin or triiodothyronine; we are trying to settle what triiodocetic acid, thyroproprionic acid, and various other analogues do. Simply to define this in terms of the amount of thyroxin getting across the placenta is probably an oversimplification. If a patient has hypothyroidism, whatever its etiology, and is given desiccated thyroid, the disease is ameliorated. However, now I think that a deficit in practically every link of the chain that I have described has been described, causing the same final clinical picture of cretinism. A cretin may have a high I^{131} uptake, but the metabolic chain stops there. A cretin may take up I^{131} and make plenty of monoiodothyronine but then apparently has an enzymatic block and cannot make diiodothyronine. Some cretins who can take up iodine make monoiodothyronine, and diiodothyronine but are unable to couple it to form thyroxin. A cretin's system may go a step further and make some material which circulates as protein-bound iodine, so there is an amazing paradox of a cretin with a high I^{131} uptake and a high protein-bound iodine who is cretinous because he is not getting adequate thyroid hormone into the tissues.

We are now attempting to define three specific binding proteins, one prealbumin, one interalpha globulin, and one albumin, all of which are very specific and which vary independently in the various thyroid states.

DR. JOHN CRIGLER.—The presence of disturbances in the newborn infants of mothers who have had thyroid disease may be the result of thyrotoxicity-producing substances crossing the placenta and causing a very hyperplastic thyroid gland in the infant. Thyroxin from the mother crossing the placenta will not do this, although it may cause thyrotoxicity. It is very important to keep hyperthyroidism of pregnant women controlled. Overtreatment of the mother's hyperthyroidism may result in hypothyroidism in the infant, particularly if antithyroid compounds are used. We recently had sent to us, from Dr. James W. Sayre in New London, Connecticut, a patient who was severely hypothyroid on the first day of life; the mother had received 300 mg. of propylthiouracil throughout her pregnancy. This child did not have an enlarged thyroid gland, yet hypothyroidism occurred.

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Comments on Current Literature

INFANTILE AGRANULOCYTOSIS OF CONGENITAL ORIGIN

IN 1956, Kostmann[1] described a newly discovered disease of infancy and early childhood termed "infantile genetic agranulocytosis" and concluded from a study of its occurrence in 9 families that the disease constitutes a clinical and a genetic entity. Kostmann used the terminology, "agranulocytosis infantilis hereditaria" and considered the condition "a new recessive lethal disease in man." He was of the opinion that this disease resulted from a primary insufficiency of the bone marrow leading to an arrest in myelopoiesis. The study included 14 children of both sexes belonging to 9 families.

The onset occurred in early infancy and the disease was characterized by failure to thrive, fever, and skin infections manifested as boils and phlegmons. In every case complete or almost complete absence of granulocytes in the peripheral blood was noted. Preparations made from bone marrow material taken at biopsy or autopsy revealed "a marked retardation or block in the maturation of the myelopoietic cells." In the absence of treatment the disease runs a short course with fatal outcome. Where infections are treated promptly and vigorously with antibiotics or chemotherapeutic agents, the affected children may survive for months or even years. However, the agranulocytosis and the deficient bone marrow remain, and Kostmann emphasized that recurrent infection is inevitable in these children, that prognosis is poor, and that fatal outcome is merely postponed. In 6 of the patients reported by Kostmann detailed clinical and histologic studies were possible. Three of the children with pronounced agranulocytosis died of severe infection before the age of 6 months. One child survived for 3 years with constant granulocytopenia, discovered at the age of 10 months, and with recurrent infection beginning at 2 months of age. The bone marrow studied by biopsy showed maturation arrest at the myelocytic stage. Cell cultures of the patient's bone marrow were undertaken, using the patient's own serum as the nutrient medium. No maturation of the myelopoietic cells could be observed. Culture of the patient's cells in normal human serum resulted in temporary activity and a fair degree of maturation. Suspecting deficiency in amino-acid complexes, cysteine was added to the patient's serum and this medium was used for bone marrow cell culture; myelopoietic cells cultured in this medium showed temporary activity and some evidence of maturation. Encouraged by this experimental result in vitro, cysteine was administered to the patient in various ways, with no improvement clinically, and no change in the histologic or hematologic findings. Two children who appeared to be suffering from a milder form of the disease were still alive at 4 years of age; these two children show periodic

granulocytopenia and have been under constant surveillance by a physician. Genetic analysis of the families involved supported "the conclusion that this disease primarily is caused by a single recessive autosomal gene difference (a simple recessive mutation)."[1] Consanguineous relationship between the parents was established in 5 of the 9 families.

Since 1956, a number of cases of congenital agranulocytosis has been reported.[2] The manifestations are similar in each instance and the disease is thought to be distinct from other leukopenic or granulocytopenic conditions in children which are transitory in nature. In all of these children recurrent infection had occurred since birth or had begun at an early age. In two reported instances the children affected suffered also from hypergammaglobulinemia.[3] In the *Acta Paediatrica* for January, 1959, an interesting and very informative case report appears. This report by Folke Hedenberg[4] is from the Children's Hospital of Hälsingborg, Sweden, and concerns a girl who developed a pronounced granulocytopenia during the first week of life in connection with an infection. This child was followed closely until her death about one year later. Delivery was described as normal, following an uncomplicated pregnancy: she was the sixth child of healthy parents. Both mother and child belonged to blood group O, Rh positive. Five siblings are living and well and have never shown any undue tendency to severe infections or skin abscesses. For the first 4 days of life the infant was in good condition, sucked well from the breast, and showed no unexpected weight change. On the fifth day she developed fever which continued through the following day. Although the general condition of the infant appeared to be unimpaired, penicillin therapy was instituted, since the pharynx and the tympanic membranes were somewhat reddened. As a diagnostic aid, lumbar puncture was performed; spinal fluid findings were reported as normal. Despite penicillin therapy, otitis media developed, and at two weeks of age paracentesis was performed. Blood examinations during this period showed the agranulocytopenia to be a constant feature of the illness, and bone marrow examination revealed an abnormal pattern. During the weeks following, otitis media persisted in spite of chemotherapy and treatment with antibiotics; at 4 weeks of age conjunctival infection occurred. During the entire 13 months of life, this child experienced severe recurrent infection, a variety of organisms being implicated. Intermittent administration of gamma globulin was added to the therapeutic regime. Pronounced agranulocytosis remained throughout the entire course. Severe skin infections accompanied by high fever were recurrent—infections of the fingers, furuncles of the thighs, the gluteal regions, and the neck. From the age of 4 months, the child was hospitalized almost continuously, being discharged on occasion when temporary improvement occurred. In the later weeks convulsions and vomiting were marked accompaniments of the illness. Spinal fluid findings were consistently normal.

With the exception of the agranulocytosis the hematologic findings were within normal limits; total serum protein levels and electrophoretic pattern were normal. The total urinary excretion of amino acids and the excretion of individual amino acids were normal. X-ray examinations of the skull, heart, and lungs revealed nothing abnormal; electroencephalographic examination gave normal findings. Extensive bone marrow studies were carried out, including bone marrow examinations at intervals and bone marrow cell cultures. Maturation arrest at the myelocytic stage was observed consistently. This block in myelopoiesis appeared to be the chief characteristic

in all the bone marrow preparations, including those made from tissue taken at autopsy. The bone marrow studies following autopsy showed a general paucity of cellular elements and an unusual accumulation of fat. No lymphocytes were observed in the bone marrow preparations. Lymph nodes showed no gross changes, and nothing remarkable was observed on microscopic study. The bone marrow cell cultures are of interest. These special investigations were carried out by Dr. P. C. Munk Plum[5] of Dianalund, Denmark, who has been interested for a number of years in the influence of the sulphur-containing amino acids on the erythropoietic activity of bone marrow cells. Samples of the patient's bone marrow were cultured in a number of ways: in her own serum; in the serum of a normal child of the same age; culture of the bone marrow of a normal child in the patient's serum; culture of the patient's bone marrow in her own serum to which tyrosine, cysteine, liver extract, or vitamin B_6 had been added. The characteristically low bone marrow activity occurring after the promyelocytic stage was increased temporarily when normal serum was used as the culture medium, with evidence of maturation and differentiation of myelopoietic cells. The addition of cysteine and vitamin B_6 to the patient's serum for culture medium brought about a similar effect. However, these substances administered to the patient in various ways did not result in any improvement. Brief therapy with ACTH did not seem to be influencing the course of the illness, and this treatment was not continued. Likewise, therapeutic attempts with cortisone, vitamin B_{12} and folacine were without effect.

After careful evaluation of this case, Hedenberg concludes that the patient's illness "is most likely analogous to that described by Kostmann in 1956."[4] However, in the single case investigated by Hedenberg no evidence of genetic factors could be elicited. Blood counts on all members of the immediate family were normal; in general the collateral families were large, as many as 10 children in one instance, all of whom were normal. No consanguinity was detected among the relationship. Hedenberg is inclined to consider this disease "a congenital defect of the patient's ability to utilize the sulphur-containing amino acids" and states that "possibly the myeloblasts do not contain enough sulph-hydryl groups, and therefore maturation and differentiation cannot reach beyond the myelocytic stage." However, as this author emphasizes, neither the true genetic nature of the condition nor the actual role of these chemical complexes in the pathogenesis of the disease can be elucidated on the basis of the few cases studied to date.

RUSSELL J. BLATTNER

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News and Notes

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Dr. Carlos Perez Trevino, 532 Minnesota, Apt. 4, Corpus Christi, Texas.

The **IX International Congress of Paediatrics** will take place in Montreal, Canada, from July 19 to 25. All forms and information may be obtained from the Secretary-General, P.O. Box 215, Westmount, Montreal 6, Quebec.

Those interested are urged to register as soon as possible as early registration ensures good accommodations.

A 3-day *seminar on Pediatric Cardiology* for pediatricians, internists, and general practitioners will be held August 16 to 19 at the **University of California** conference center at Lake Arrowhead, 85 miles east of Los Angeles.

Guest speaker at the seminar, sponsored by the UCLA School of Medicine and University Extension, will be John Lind, M.D., head of the department of pediatrics at the University of Stockholm.

The Pediatric Cardiology seminar will be followed by seminars on Emotional Problems in Office Practice August 19 to 23 and Internal Medicine, August 23 to 26.

Information and applications may be obtained from the Department of Continuing Education in Medicine, UCLA Medical Center, Los Angeles 24, Calif.

Traineeships in Cardiovascular Research, in either clinical pediatric cardiology or pertinent basic sciences, are available for qualified persons at the **Childrens Hospital of Los Angeles** for one year, with the possibility of extending them to two or three years.

Skills in pediatric cardiology are emphasized for first-year clinical trainees, although they may participate in selected supervised clinical studies. Second-year clinical trainees assume greater responsibility in clinical training and spend up to half the time in supervised research with increasing independence. Third-year trainees spend the majority of time in research while maintaining close contact with clinical activities. Teaching responsibilities are scaled accordingly.

Further information and applications should be addressed to Department of Pediatrics, Childrens Hospital Society of Los Angeles, 4614 Sunset Boulevard, Los Angeles 27, Calif.

The **Denver Children's Hospital** eleventh annual Summer Clinics will be held June 24 to 26, 1959. J. Roswell Gallagher, M.D., Chief of the Adolescent Unit, Boston Children's Hospital; F. Howell Wright, M.D., Professor and Chairman of the Department of Pediatrics, University of Chicago School of Medicine; and Judge Leo B. Blessing, LL.D., Judge of the Juvenile Court, New Orleans are the guest faculty members.

In addition to discussing recent developments in general pediatric care, the social and medical problems the teenager must adjust to, or overcome, before finding acceptable status in the community will be examined.

Cost of the course, including luncheons and banquet, is $35.00. Further information may be secured by writing to the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

The District of Columbia **Children's Hospital Variety Club Research Center,** commemorating the Variety Club's former chief barker, Fred S. Kogod, was dedicated in March. Director of the Research Foundation which was incorporated in 1947 to further pediatric research at Children's Hospital is Dr. Robert H. Parrott, Physician-in-Chief of Children's Hospital.

Books

Clinical Radiology of Acute Abdominal Disorders. Bernard Epstein, M.D., Philadelphia, 1958, Lea & Febiger, 352 pages. Price $15.00.

Dr. Epstein shows a breadth of knowledge and familiarity with the current thinking in his particular field of medicine. This volume is a guide to disorders involving the structures between the diaphragm and the pelvic floor. The subject is presented on the basis of abdominal complaints and is not limited to those dramatic and urgent conditions which are ordinarily labeled "the acute abdomen."

The descriptions are brief, accurate, sharply drawn, and provide in concise detail the essential features of each entity. The style is simple, clearly stated, and without adornment. Discussions of each topic correlate the clinical, pathologic, and roentgenologic manifestations of the disease. These facts are developed in a logical fashion, providing an excellent thumbnail sketch of the disease entity.

The introductory chapter begins with a discussion of embryologic factors which sets the background for the consideration of congenital disorders. The book is organized according to an etiologic scheme, covering the four major categories of abdominal pathology: chapter I, congenital disorders; chapter II, neoplastic diseases; chapter III, inflammatory diseases including parasitic and granulomatous diseases, collagen disturbances, metabolic disturbances, vascular disorders; chapter IV, traumatic disorders: foreign bodies and effects of drugs.

Within these major groupings the discussions are arranged according to organ systems in a logical manner. For example, under neoplastic diseases, tumors of the stomach, duodenum, small bowel, appendix, and colon are taken up in succession, followed by those of the biliary tree, ampula, liver, pancreas, spleen, etc. Under inflammatory diseases, the same arrangement by organ systems is used. Toward the end of this chapter systemic diseases and diseases of specific etiology such as parasitic, fungus, virus, tuberculosis, syphilis, etc. are taken up categorically.

The illustrations are well chosen and maintain good definition and detail upon reproduction. Approximately 400 roentgenograms have been reproduced. Sharp reference lists and suggestions for additional

reading are appended to each section. These are few in number but are a sufficient introduction to the pertinent subject matter. Although the author's purpose is well accomplished within the structure and format of this book, one would like to see a little more attention given to the technical aspects of the abdominal and gastrointestinal examination. Such a discussion would, of course, have greater interest for the radiologist than for the clinician, but it would enhance the value of this book as a reference text.

Bernard S. Loitman, M.D.
St. Louis, Mo.

Amino Acids and Peptides With Antimetabolic Activity. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, Ciba Foundation Symposium, Little, Brown & Co., Boston, 1958, 286 pages. Price $8.75.

There are, in general, two ways in which to present a review in a field of scientific endeavor. In the first of these, one or more authors attempt to reduce to one article the known aspects and findings of the particular field. In the second, as is the case here, a group of distinguished scientists are called together to elaborate more fully on their own particular findings within the general framework of the subject. This second approach may lack completeness of coverage, but more often than not it makes for more interesting and informative reading.

This Ciba Foundation Symposium contains much information that is necessary for the biochemist and oncologist. The main part of the book is devoted to the presentation of findings on a host of compounds such as amino acid derivatives of the nitrogen mustards, azaserine, 6-diazo-5-ozo-L-norleucine, and the antibiotics, chloramphenicol, actinomycin, etamycin, and bacitracin. The organic chemist will also find some very interesting work concerning the structure of some of the polypeptide antibiotics as well as studies on the mechanism of polypeptide synthesis.

The general practitioner may find much of this volume outside the scope of his usual reading matter. However, he might be well advised to glance through some of the sections dealing with the mode of action of tumorocidal agents. In particular, the general discussion found between pages 185 and 191, in which the participating members of the Symposium give free rein to their thoughts concerning the ability of some compounds to inhibit tumor growth, are highly recommended as an introduction to the literature on current thoughts on this subject. This book belongs on the shelf of the specialists and should be referred to with more than passing interest by the practicing physician.

Victor H. Auerbach, Ph.D.

Erratum

In the article by B. M. Kagan, M.D., and Natalia Felix-Balcom, M.D., "Intravenous Chloramphenicol in Seriously Ill Infants and Children," in the April, 1959, Journal, on page 480, the second column, the second sentence of the last paragraph should read, "One was in a patient who was given undiluted 'Chloramphenicol Solution.'"

Editor's Column

THE PREMATURE INFANT

THIS issue of THE JOURNAL features a number of papers* concerned with various problems of the prematurely born infant. For the past two decades, efforts to improve the lot of the premature infant have been concentrated on methods to create an environment most favorable to the infant's extrauterine growth and development. The Children's Bureau has been most active in providing leadership and support in this effort. The review of 10 years' experience in New York City is of historical and current interest. Other states and cities have tried other types of approach. Massachusetts encouraged and assisted in the establishment of approved premature nurseries in key areas throughout the state and underwrote some of the training for nursing and pediatric personnel to staff these nurseries. Today, almost every state and city have some program in operation designed to improve the care of the premature infant. The American Academy of Pediatrics' widely accepted standards for the care of both premature and full-term infants also have been of real help in safeguarding the premature infant. There can be no doubt but that all of these endeavors have been of value in saving a certain number of infants and there has been some decrease in the mortality rates of premature infants. In this regard the establishment of approved nurseries has been an important factor, although there have been many other contributing factors such as the general elevation of the standard of living, the introduction of antimicrobial therapy, and many improvements in obstetrical management.

The discouraging aspect of the situation in regard to premature infants remains the fact that to benefit from the "care programs" the infant must live long enough to enjoy them. The brutal facts are that prematurely born infants constitute nearly 60 per cent of the neonatal mortality and from 60 to 80 per cent of the deaths of premature infants occur in the first 48 hours of life, prior to the time the "care program" could exert its influences. Dr. Herman Bundensen's statement is still true: "There has been no reduction in natal day deaths in forty years." Furthermore, no clinic has been able to reduce the mortality rate of premature infants below 15 per cent.

The problem would be resolved if we could eliminate premature labor; it could be vastly improved if we could lower the incidence of this condition. However, the average incidence continues to be 6 to 8 per cent of live births. With 4½ million live births

*Papers one to four inclusive.

a year in the United States, this means 270,000 to 360,000 infants will be born prematurely. Silverman confirms, what many other follow-up studies have found, that thorough examination of surviving premature infants at 2 years of age reveals a 25 per cent incidence of significant neurologic disorders or mental retardation. He concludes that the problem of brain damage in premature infants is one which requires at least equal consideration with the problem of reducing their mortality rate.

The hope for improving the prematurely born infant's outlook for life, liberty, and the pursuit of happiness would appear to lie in research into the many perinatal factors that may influence morbidity and mortality. This approach is comparatively new and arises from the realization that those factors responsible for the death or injury of the infant a short time before birth must be the same factors operating in the early hours of life. It was not so long ago that the care of the premature infant was surrounded with mystery and the premature nursery was enclosed by a nursing iron curtain through which few pediatricians could penetrate. Believe it or not, this amazing situation still exists in some of the "best" hospitals. Fortunately, the natal and neonatal field, one of the few remaining frontiers for research, is being increasingly explored by scientific investigators. One has but to consider the contributions in this area that appear each month in our pediatric and obstetric journals and witness the large number of original papers on this subject on the programs of our research societies to appreciate the army of physicians and allied scientists who are working to the ultimate benefit of the premature infant.

One cannot help but feel confident that we are living in the decade in which we will witness a major breakthrough in the search for means to solve the problems of the prematurely born infant.

Stewart H. Clifford

GREETINGS TO THE IXTH INTERNATIONAL CONGRESS OF PEDIATRICS

THE Editorial Board of THE JOURNAL takes this opportunity to extend greetings and best wishes to Dr. Alan Ross and his planning and managing committees for the meeting of the International Pediatric Congress in Montreal July 19 through 25.

The program committee under the leadership of Dr. Harry Ebbs has spared no effort to develop a scientific program which should justify the assemblage of pediatric leaders from all countries of both hemispheres. One unique feature will be the availability of rooms for group discussions or forums which may be generated during the week of the Congress and can be arranged for "on the spot."

The Editorial Board of THE JOURNAL is pleased to have had the opportunity to make a small contribution to the Congress by helping to defray the expenses of several of the program participants from other countries.

International meetings, as do certain of the local ones, have a dangerous potential to degenerate into little other than vacation junkets. It would seem reasonable to examine the reasons for holding international medical meetings, specifically pediatric ones.

We believe there are substantial reasons in favor of triennial assemblages of medical educators and investigators whose interests are in the same general field of medicine. Perhaps the principal ones are the opportunities to share experiences in open forums and in private discussions. By such means men are stimulated, ideas are generated, and cooperative research can be initiated and planned to make use of related clinical material in different environmental settings. If these are the principal justifications, and we believe they are, then we would reiterate our faith in the pediatric world by stating that we believe we have as good or better chances of attaining these goals than do other clinical divisions of medicine.

International health and international economy are factors basic to international understanding and to peaceful and profitable cohabitation by the peoples of the world. The health of children in all countries, but especially in the presently underprivileged countries, constitutes a major problem. Pediatrics must assume the major responsibility.

Lest we be misunderstood concerning the social aspects of such meetings, may we add with deep conviction that without them there is only sterility and failure. But we need not be concerned on this score. It is not possible for men of good will to assemble without forming new friendships, and in this particular instance of renewing old ones. Personally we are looking forward to seeing again our friends from many countries—on occasion in more congenial settings than assembly halls.

So to our Canadian hosts, hail and good meeting! We look forward to our visit with anticipation and in confidence.

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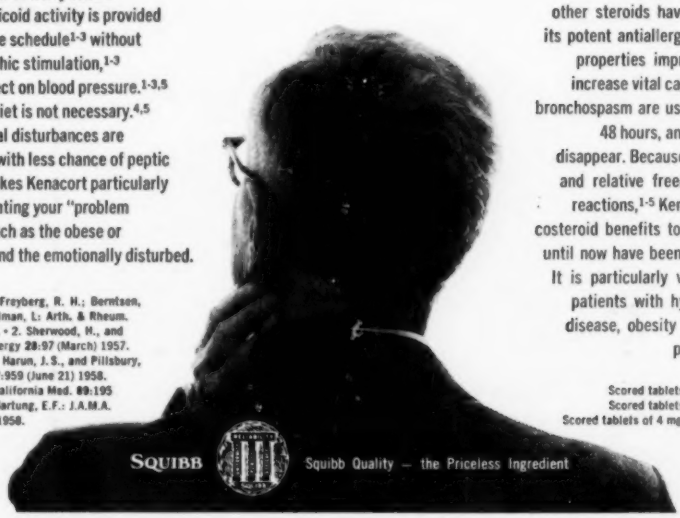

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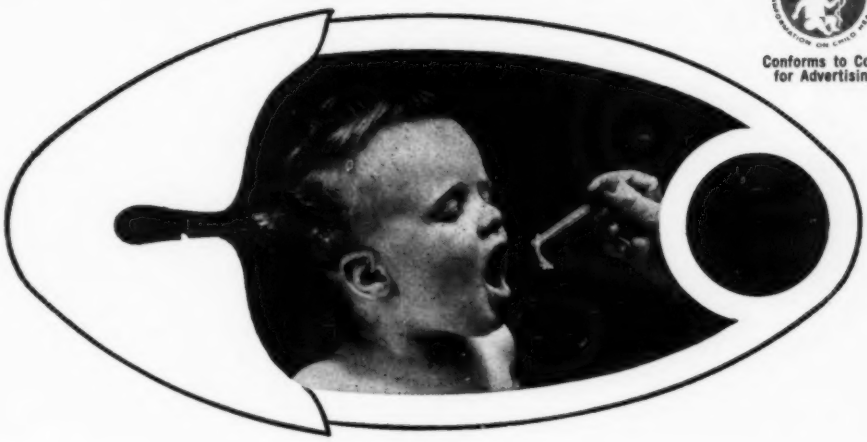

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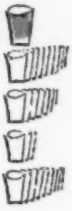

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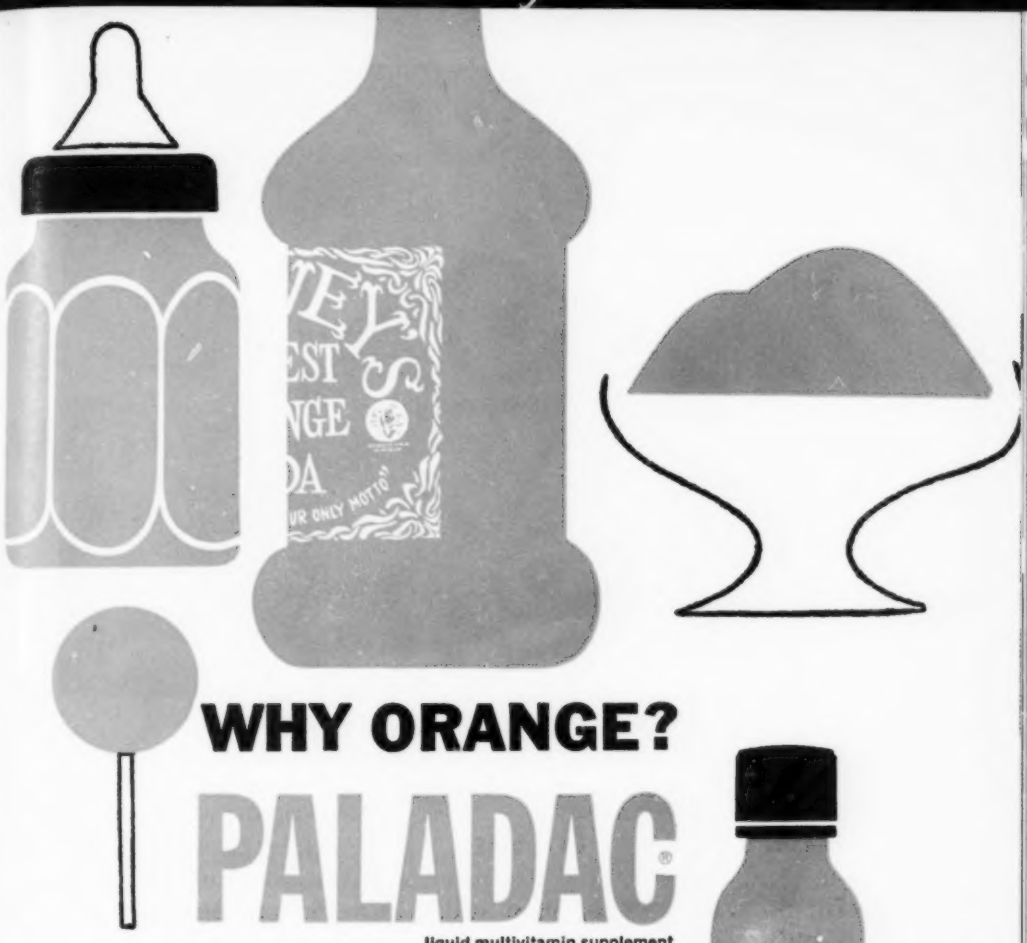

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1. Tuttle, A. H., and Etteldorf, J. N.: J. Ped. 41:170, 1952. 2. Kelly, H. T.: Pennsylvania M. J. 51:999, 1948.

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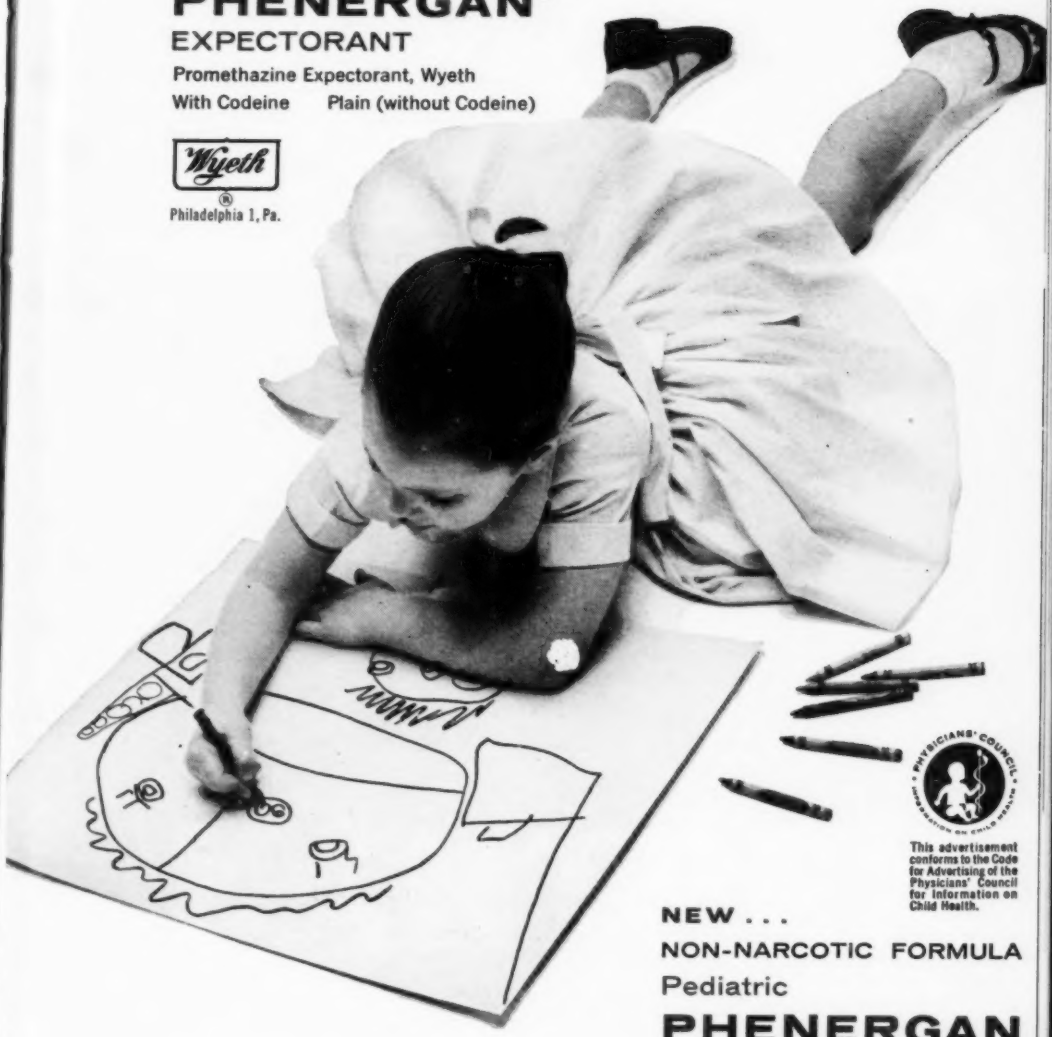

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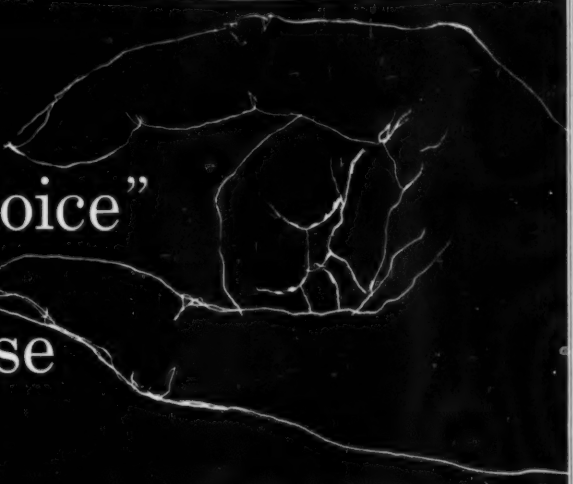

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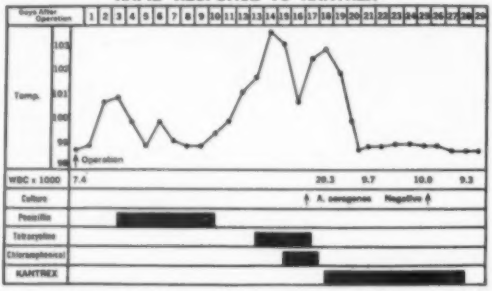

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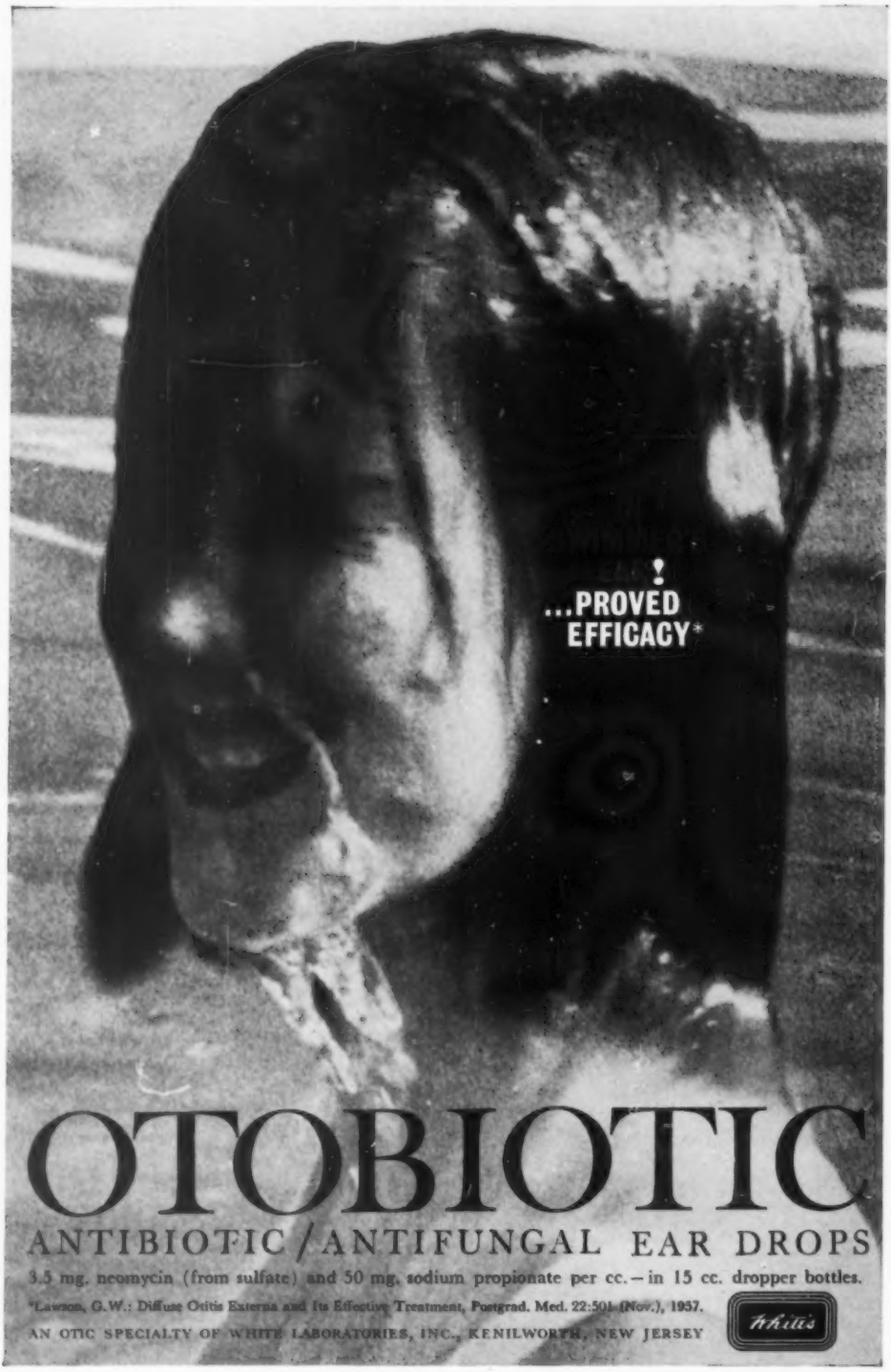
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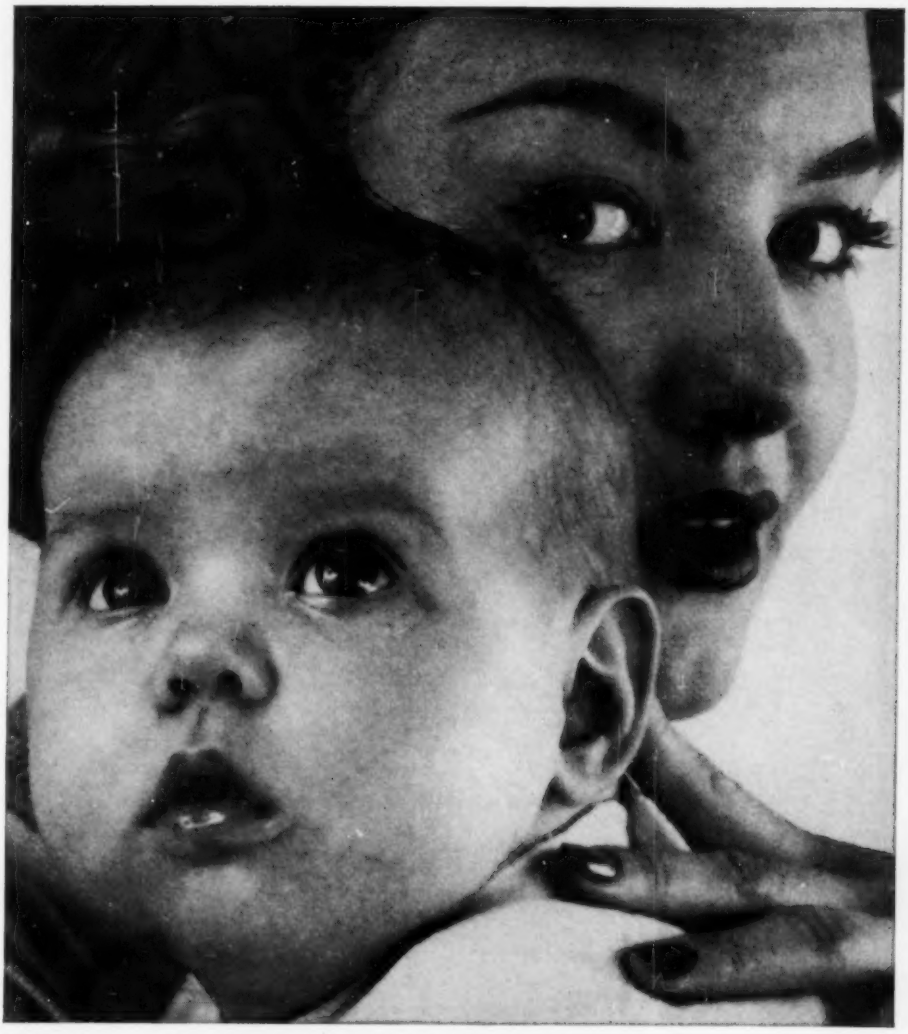

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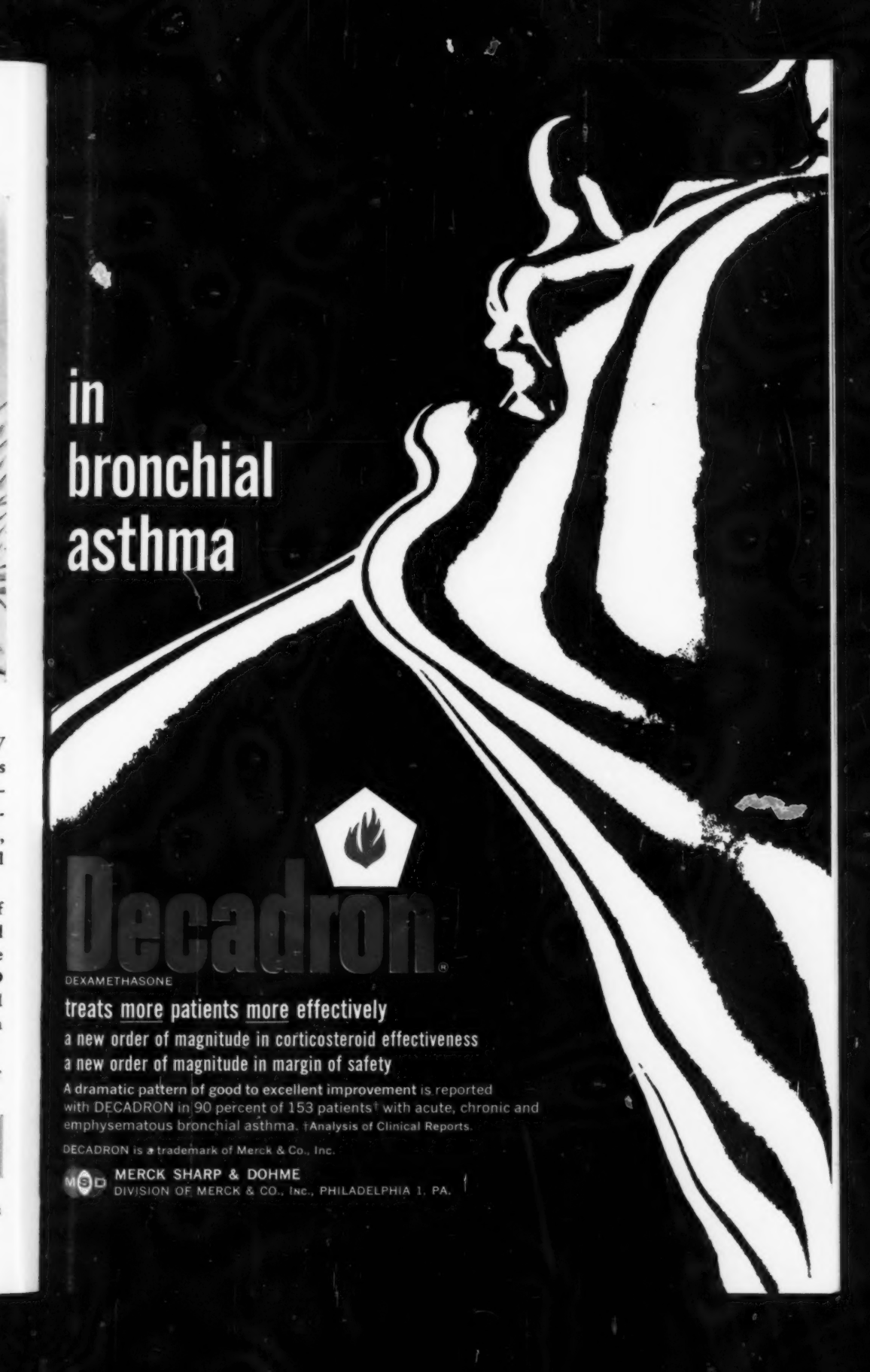
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ANTINAUSEA SUPPRETTES (Children)
Require no refrigeration.
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The "Neocera" Base Makes the Difference
Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes readily with rectal fluids.
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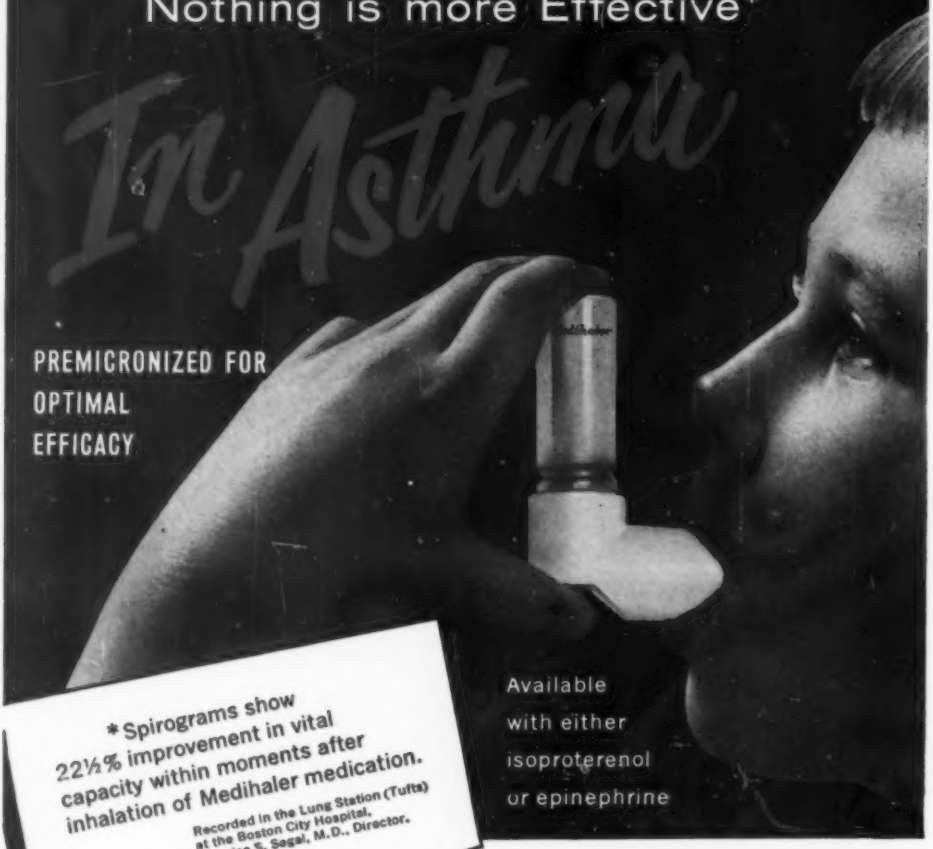

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Baby's sensitive skin is best protected by the use of **ACID MANTLE – CREME or LOTION – pH 4.2.** It instantly restores normal acidity to the skin which has been made alkaline, due to contact with urine. It thus prevents diaper rash.

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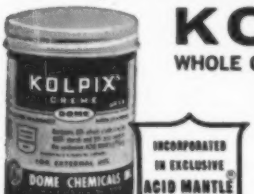

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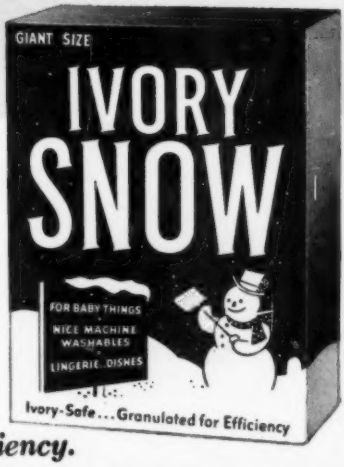

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Nitrogen retentions of infants fed breast milk or Similac were compared in the Metabolism Ward of the University Hospital at Iowa City – a homelike yet controlled environment. No solid foods were fed. Three-day balance studies were carried out on each infant approximately every 2 weeks for 6 months.

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"It is therefore concluded, as judged by these criteria, that the infant's requirement of protein from cow's milk is no greater than that supplied by ad libitum feeding of Formula S."[4]

References: 1. Fomon, S. J., and May, C. D.: Pediatrics *22*:101 (July) 1958. 2. Fomon, S. J.; Thomas, L. N., and May, C. D.: Pediatrics *22*:935 (Nov.) 1958. 3. May, C. D.: Pediatrics *23*:384 (Feb.) 1959. 4. Fomon, S. J., and May, C. D.: Pediatrics *22*:1134 (Dec.) 1958.

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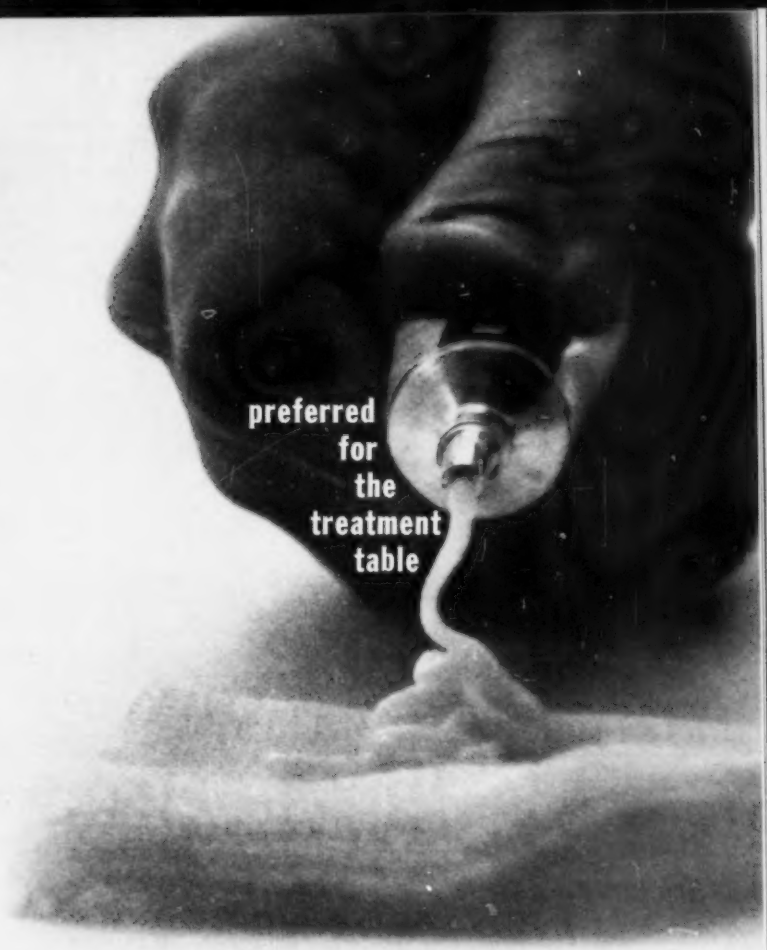

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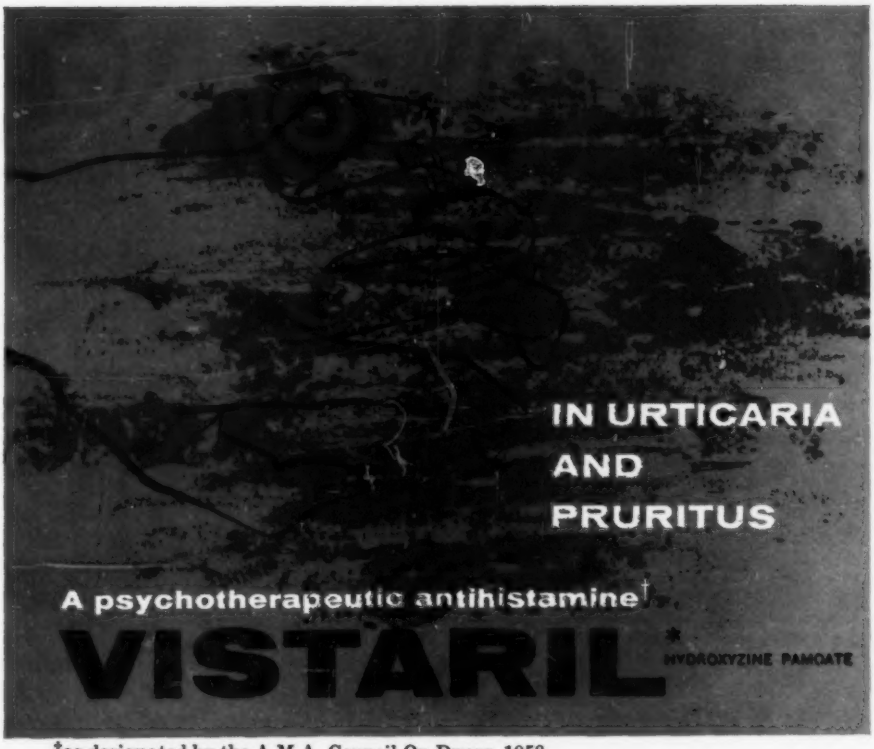

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reduces—erythema, excoriation and extent of lesions.[1-4]

Recommended Oral Dosage:
50 mg. q.i.d. initially; adjust according to individual response.

References: 1. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 2. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958. 3. Robinson, H. M., et al.: J.A.M.A. *161*:604-606 (June 16) 1958. 4. Robinson, H. M., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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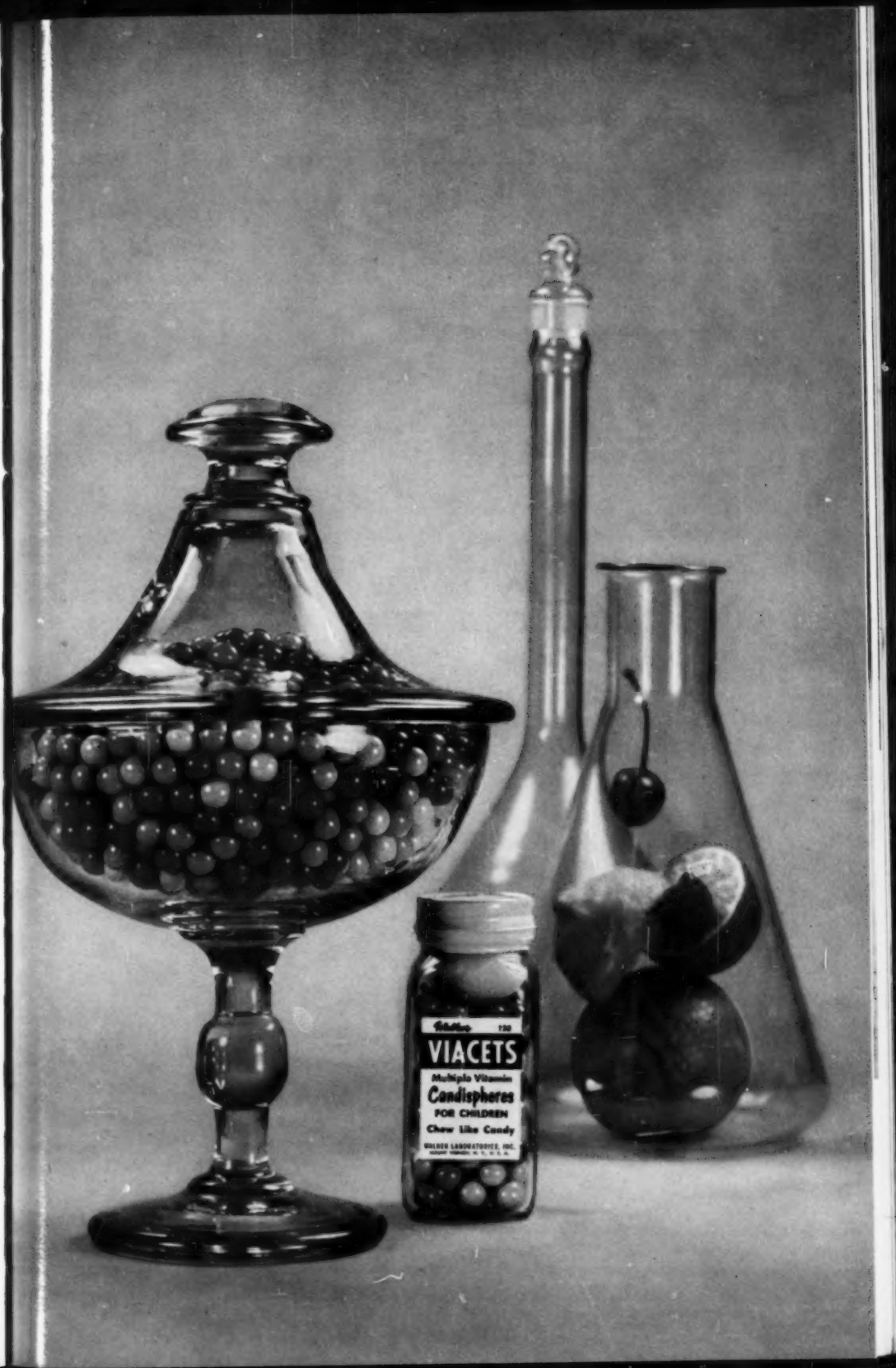
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These antihistamines block the effect of histamine on the nasal and paranasal capillaries, preventing dilation and exudation.[3] *This is not enough;* by the time the physician is called on to provide relief, histamine damage is usually present and should be counteracted.

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TRIAMINIC is orally administered, systemically distributed and reaches *all* respiratory membranes, avoiding nose drop addiction and rebound congestion.[6,7] TRIAMINIC can be prescribed for prompt relief in summer allergies, including hay fever.

References: 1. Sheldon, J. M.: Postgrad. Med. 14:465 (Dec.) 1953. 2. Hubbard, T. F. and Berger, A. J.: Annals Allergy p. 350 (May-June) 1950. 3. Kline, B. S.: J. Allergy 19:19 (Jan.) 1948. 4. Goodman, L. S. and Gilman, A.: Pharmacol. Basis Ther., Macmillan, New York, 1956, p. 532. 5. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958. 6. Lhotka, F. M.: Illinois M.J. 112:259 (Dec.) 1957. 7. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958.

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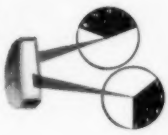

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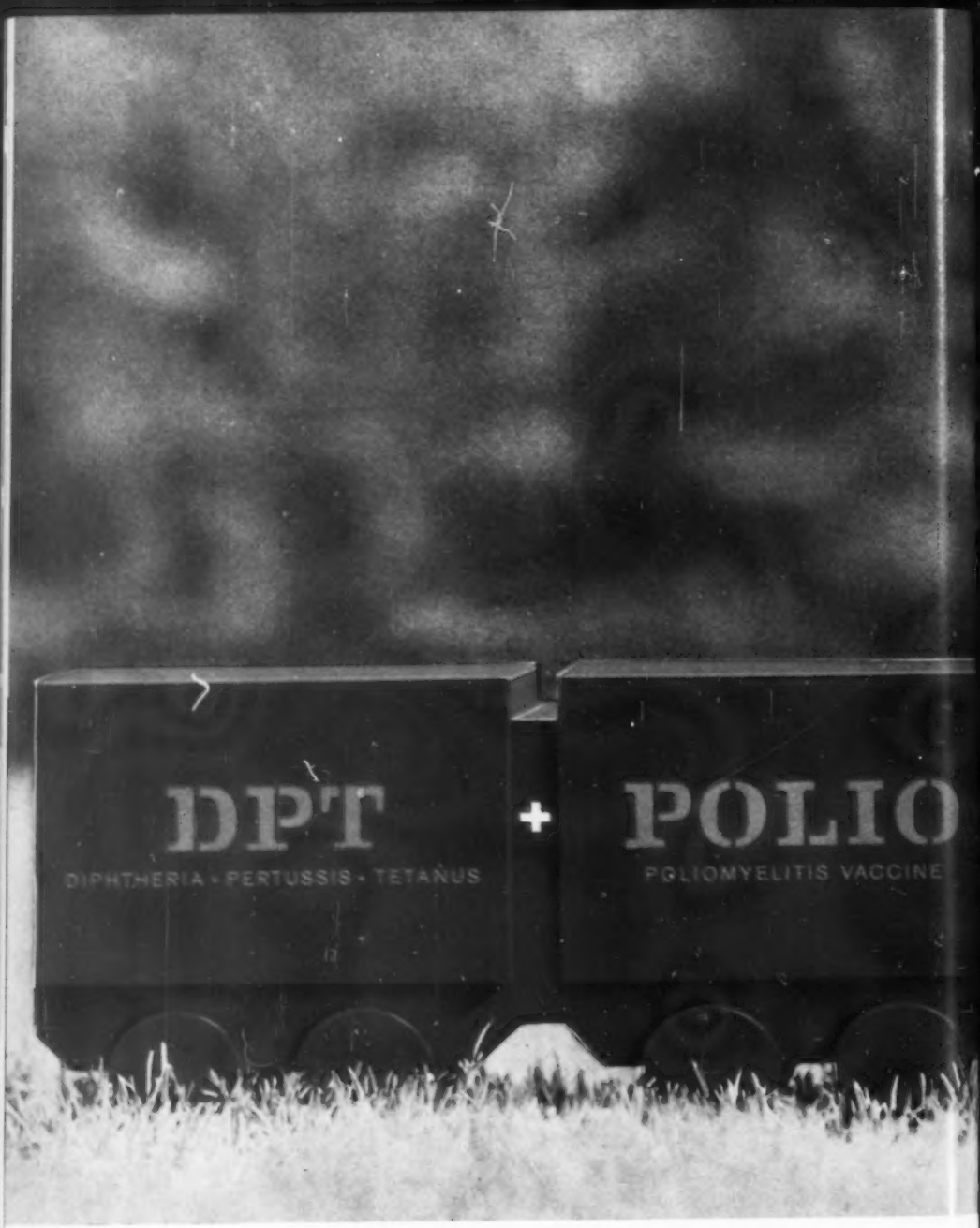

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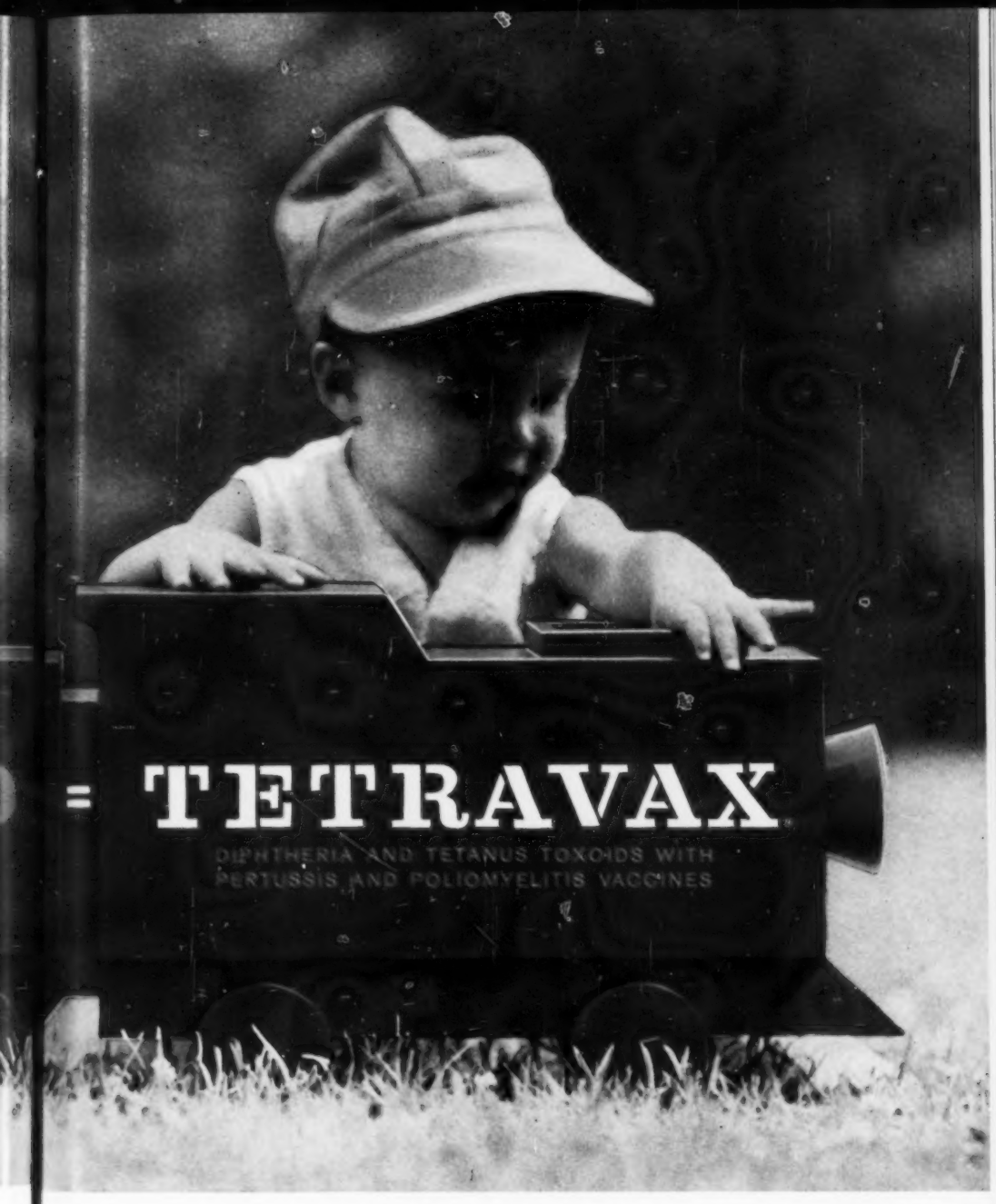

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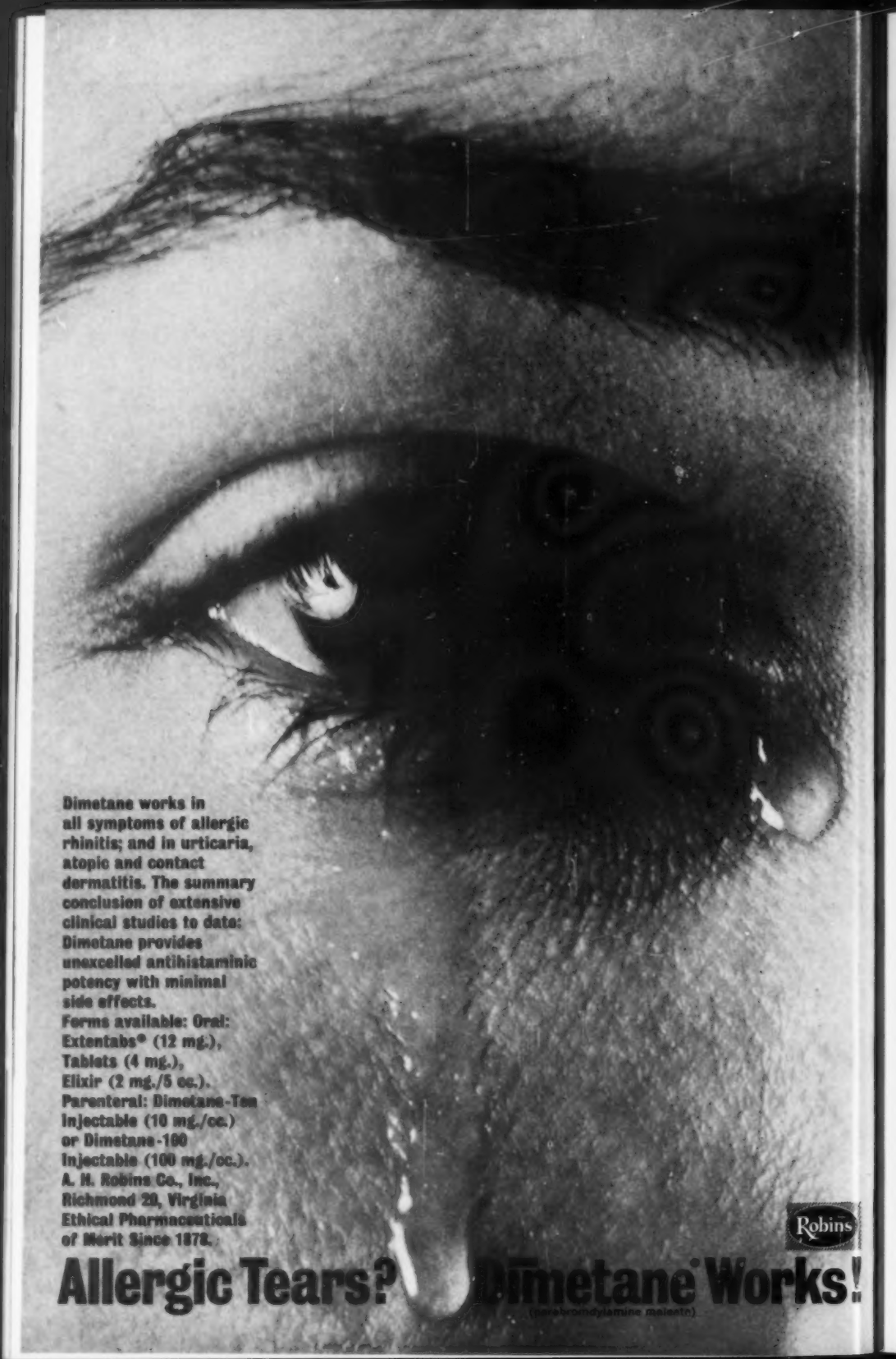
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IMPORTANT: Do not dilute or take other fluids immediately before or after each dose.

Supplied: Bottles of 3 fl.oz. and 16 fl.oz.

1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
2. Bradley, J. E.: Mod. Med. 20:71, No. 20, 1952.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

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1. Frank, L.: Research Report 1.35

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Galeota, W. R., and Moranville., B. A.: Student Medicine (in press)

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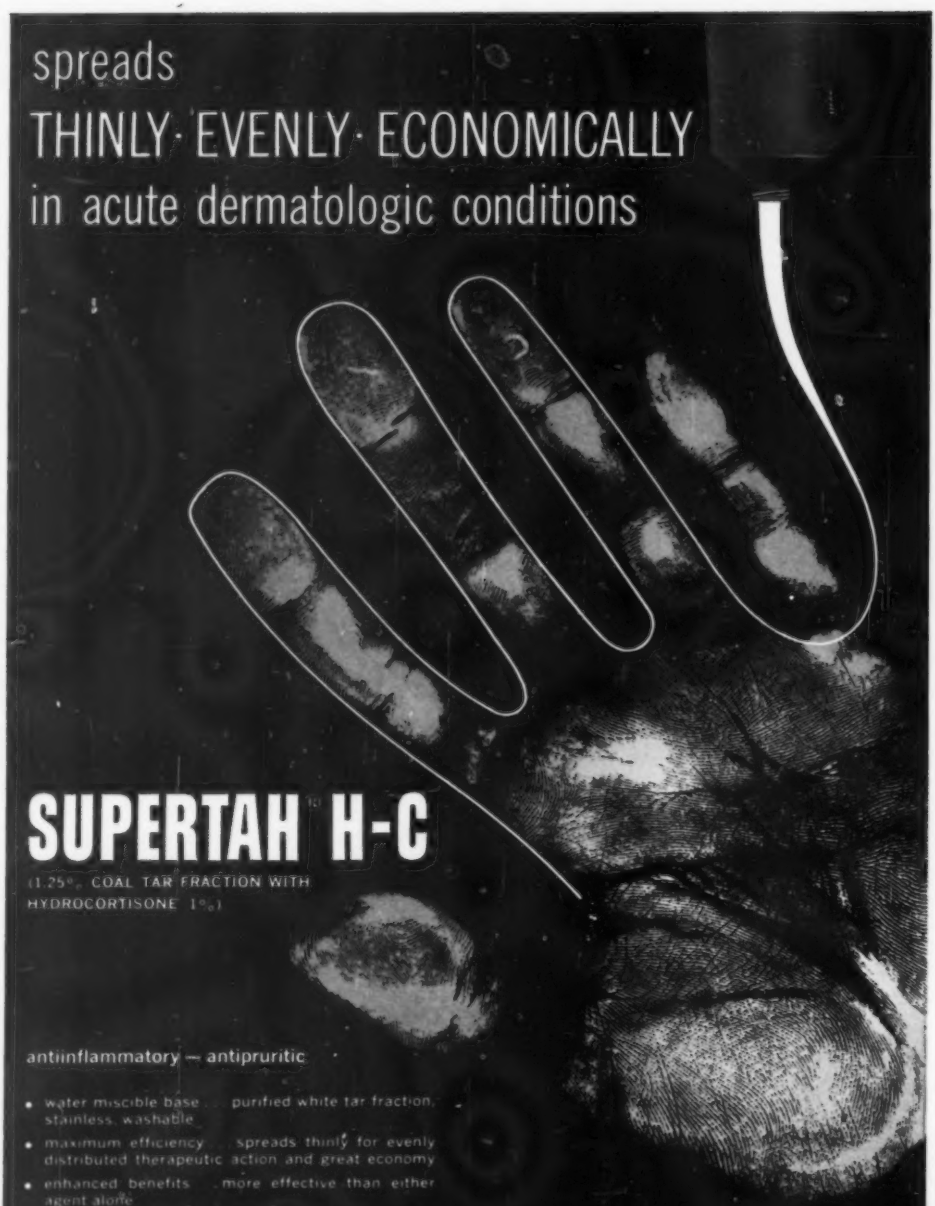

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- water miscible base . . . purified white tar fraction, stainless, washable
- maximum efficiency . . . spreads thinly for evenly distributed therapeutic action and great economy
- enhanced benefits . . . more effective than either agent alone
- excellent response . . . deep penetration to source of inflammation

supplied: ½-oz. tube

also available:
SUPERTAH Ointment (1½-oz. tube)
provides the therapeutic effectiveness of time-proved tar medication
SUPERTAH S/S (with salicylic acid and sulfur; 1½-oz. tube)
for keratolytic action

All Supertah preparations are made with refined natural coal tar fraction

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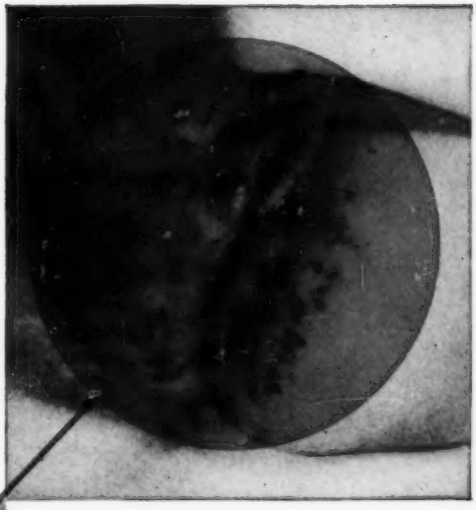
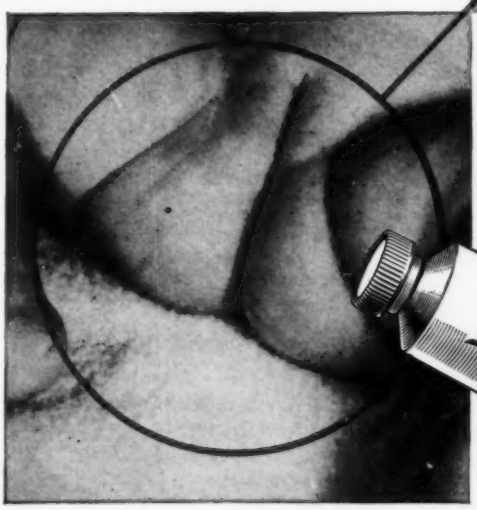
Effective treatment and prevention of Diaper Rash





Diaparene® Chloride Ointment (Brand of methylbenzethonium chloride) 93% effective in the treatment of ammonia dermatitis.[1] The case illustrated cleared in 4 days.

1. Niedelman, M. L. and Bleier, A.; Jrnl. Ped. 37:762, 1950.

Supplied:
1 oz. tubes
2 oz. tubes
4 oz. tubes
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LITERATURE AND SAMPLES ON REQUEST

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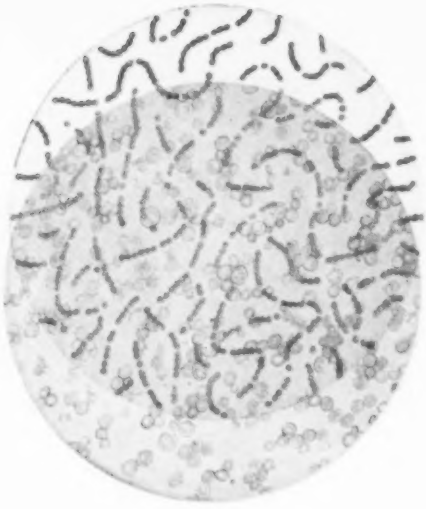
eradicate bacterial infection

prevent monilial superinfection



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250 mg. glucosamine-potentiated tetracycline (Cosa-Tetracyn®) plus 250,000 u. nystatin

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MEDICATED
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POWDER AND LOTION

1. Koessler, H. W.: Arch. Ped. 74:47 (Feb.) 1957.
2. Kahan, H. *et al.*: Arch. Ped. 73:125 (Apr.) 1956.
3. Editorial: J.A.M.A. 165:254 (Sept. 21) 1957.

active ingredients:
glyoxyl diureide
dimethylpolysiloxane
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WHEN THE BABY HAS COLIC "...AND

SCREAMS

WITH THE OUTRAGED VIGOR OF A WOUNDED TIGER AND PUNCTUATES HIS SHRIEKS WITH FLATUS..."*

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Methyl Scopolamine Nitrate

FOR THE TREATMENT OF INFANT COLIC

Easy Administration: Just one or two drops of Skopyl under the tongue, 20-30 minutes before each feeding — or 3 drops for an acute attack of colic.

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*Editorial: New England J. Med. 260:246 (Jan. 29) 1959

Precautions: Fluid balance should be restored in dehydrated infants or those with oliguria before beginning treatment with Skopyl. **Indications:** Colic (paroxysmal fussing, infantile dyspepsia, irritable crying), infantile vomiting, infantile diarrhea, pyloric spasm. **Available:** 5 cc. dropper bottle. One drop=0.6 mg.; 40 drops=1 cc. **Pharmacia Laboratories, Inc.,** 501 Fifth Avenue, New York 17, N.Y.

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AVEENO® Colloid Baths

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Aveeno colloid baths bring immediate relief to itching inflamed skin; they are specific supportive therapy to slower-acting internal steroids.

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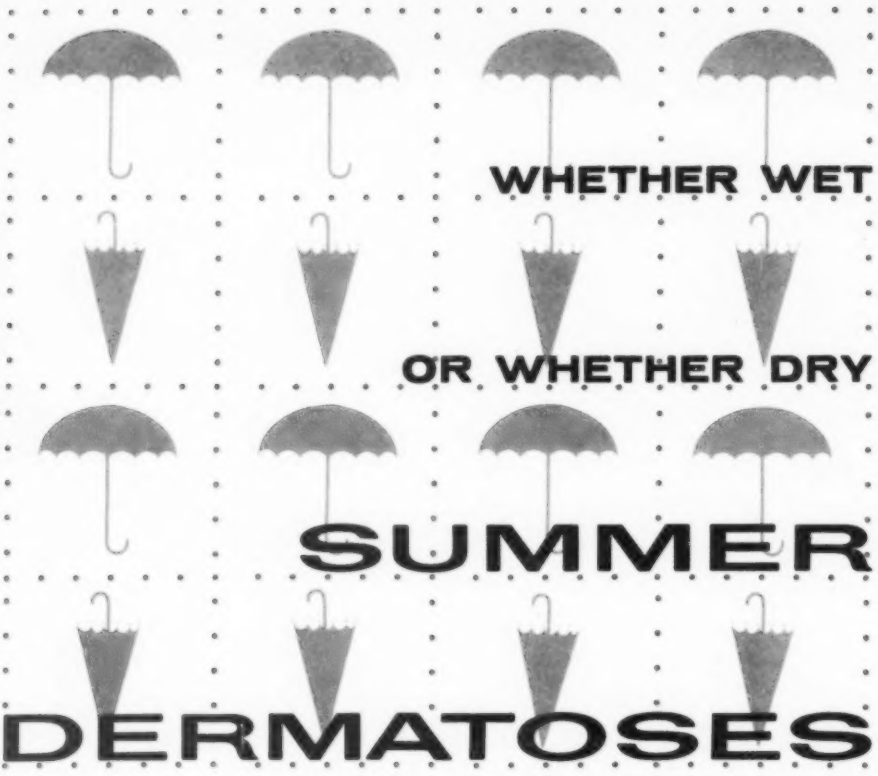

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such as poison ivy, sunburn and prickly heat promptly respond to soothing

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reduces inflammation... relieves pruritus...
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MALT SOUP EXTRACT
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Malt Soup Extract is a non-diastatic barley malt extract neutralized with potassium carbonate. It's harmless and, when necessary, can be given over a long period of time without any side effects. It causes no inflammation, no gas pains and restores a normal acid condition in the lower tract.

For babies two tablespoonfuls of Malt Soup Extract is added to the formula. For children two tablespoonfuls in milk (children love it) twice a day or use it on cereals or in fruit juice.

Some physicians prefer the liquid form. Many like the mild tasting, easily handled powder form. Both are available at drug stores coast to coast.

8 oz. and 16 oz. bottles.

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SQUIBB MULTIPLE VITAMIN SOFT TABLETS

fruit-punch flavored tablets that will actually "melt in the mouth"

can be chewed like candy

can be crushed and sprinkled on cereal or other food

can be dissolved in water, juice or milk

can be sucked and will dissolve like a lozenge

can be easily swallowed (small tablet size)

VIGRAN CHEWABLES *taste like candy,* but contain *no ingredients harmful to teeth.* Important, too, is that VIGRAN CHEWABLES *dissolve easily* in the mouth and *smell good.* And VIGRAN CHEWABLES provide at least 125% of the minimum daily requirements for vitamins A, D, B_1, B_2, niacinamide and C, and significant amounts of other essential vitamins.

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Vitamin A	5,000 U.S.P. units
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chelate "packaging" protects against iron loss or irritation in transit through g.i. tract **...may be given with meals or ulcer medication without loss of therapeutically available iron... or may be taken on an empty stomach without irritation** *—because chelated iron is not ionized and resists precipitation by alkali, protein, phosphate, or phytate.*

chelate "packaging" ensures physiologic acceptance of iron on delivery to intestinal mucosa... **proved clinically effective in moderate or severe hypochromic anemia' yet minimizes risk of toxicity on accidental overdosage** *—because chelation keeps iron in solution over an extended mucosal area for rapid uptake as required, yet inhibits excessive diffusion of iron into the circulation.*

CHELATED IRON
clinically superior in toleration, safety, and physiologic uptake

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TABLETS
SYRUP
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Supplied: FERROLIP TABLETS, SYRUP, and PEDIATRIC DROPS. Daily adult dose of 3 tablets or 1 fl.oz. syrup provides equivalent of 120 mg. elemental iron. Bottles of 100 and 1000 tablets; syrup in pints and gallons. Each cc. of pediatric drops provides 25 mg. elemental iron. In 30-cc. unbreakable plastic squeeze bottles.

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*CHELATION: "a well-recognized chemical process wherein metallic ions are sequestered and bound into claw-like rings within the chelating molecule... Hemoglobin has long been recognized to be a chelate complex of iron..."[1]

1. Franklin, M. et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, 1958.

Flint, EATON & COMPANY
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Squibb Triple Sulfas — Trisulfapyrimidines

THE TRIPLE SULFONAMIDE OF CHOICE IN COMMON URINARY, RESPIRATORY, AND OTHER BACTERIAL INFECTIONS

for effectiveness...
Prompt, high blood levels[1,2]
Excellent tissue diffusion[3]
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Terfonyl is economical to prescribe for your patients

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Good tasting, raspberry-flavored suspension appealing to all age groups—particularly the young and elderly patients

Supply:
Raspberry-flavored suspension, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per teaspoonful (5 cc.). Pint bottles.

Tablets, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per 0.5 Gm. tablet. Bottles of 100 and 1000.

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Pentid-Sulfas: Each tablet contains 200,000 units of crystalline penicillin G potassium and 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine. Bottles of 30, 100 and 500.

References:
1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Company, 1957, p. 232. 2. Sophian, L. H.; Piper, D. L., and Schneller, G. H.: The Sulfapyrimidines, New York, A. Colish, 1952, pp. 70-76. 3. Lehr, D.: New York J. Med. 50:1261 (June 1) 1950.

SQUIBB

Squibb Quality / the Priceless Ingredient

"TERFONYL®" AND "PENTIDS®" ARE SQUIBB TRADEMARKS

for
season-long
immunity
to poison ivy
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poison oak

make their summer carefree with **AQUA IVY, AP®**

alum precipitated pyridine-ivy extract suspended in saline solution

Good to excellent results — up to 93% of cases.[1-4]

"... superior to either alcohol/ether or the oil resorption materials because of the ease of its administration, its concentrated dosage, and its more effective clinical results along with lessened possibility of exacerbations of symptoms. The alum precipitated material is slowly absorbed".[2]

Non-toxic — non-irritating
"... even when administered to children ...".[3]

HOW SUPPLIED In a combination package containing one 5 cc. vial of a 1:50 dilution (0.3 mg./cc.) and one 10 cc. vial of a 1:5 dilution (3.0 mg./cc.) (administration sufficient for at least 3 patients).

REFERENCES

1. Gaillard, G. E.: New York J. Med. 56:14, 1956.
2. Passenger, R. E., Spain, W. C. and Strauss, M. B.: J. Allergy 27: 409-423, 1956.
3. Fontana, V. J.: GP 10:47, 1954.
4. Gaillard, G. E.: J. Allergy 21:55, 1950.
5. Strauss, M. B. and Spain, W. C.: J. Allergy 17: 1-10, 1946.
6. Heiderff, H. A.: Personal Communication.

Also available as AQUA IVY, AP® TABLETS for oral prophylaxis in bottles of 100 tablets of 0.6 mg. each. Each tablet contains 0.6 mg. dry alum precipitated pyridine-ivy.

Literature on request – WRITE TO DEPT. MJ

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and Fat in the American Diet

In this era of public concern over the possibly deleterious influence of dietary fat on human health, a sober look at the facts as they exist today appears indicated.

After reviewing the evidence up to 1958, The Food and Nutrition Board of the National Research Council* defined the contribution of fat to American nutrition.

> "The human requirement for fat or for specific fatty acids, as well as the nutritional implications of a high content of fat in the diet, remains to be determined.
>
> "In the United States an average diet containing approximately 40 per cent of the calories in the form of fat has been consistent with the attainment of one of the best health patterns in the world."

This statement by unbiased authority demonstrates that drastic curtailment of fat intake is not indicated on the basis of current evidence.

However, if special circumstances call for curtailment of fat intake, meat need not be denied the patient. Visible fat can be removed easily. In addition to its high protein contribution to tissue repair and maintenance, meat provides the gamut of B vitamins and important minerals essential to sound nutrition.

*The Role of Dietary Fat in Human Health: A Report of the Food and Nutrition Board, National Academy of Sciences—National Research Council, Washington, D. C., Publication 575, 1958.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
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as they like it...
cherry-flavored
syrup
pediatric drops
as they need it...

ACHROMYCIN® V
Tetracycline with Citric Acid Lederle

- broad spectrum control of more than 90 per cent of antibiotic-susceptible infections seen in general practice[1]
- fast, high concentrations in body fluids and tissues
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ACHROMYCIN V: 10 cc. plastic dropper bottle for precise dosage; 100 mg. per cc. (20 drops). *Dosage:* one drop per pound body weight per day.

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1. *Based on six-month National Physicians Survey.*

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(Aqueous Polyvitamin)

DROPS

- completely water-soluble... including vitamins A and D
- 3 to 5 times better absorbed, utilized, and stored than from oily media
- deliciously orange-flavored... a treat for infants and growing children
- backed by years of clinical study and pediatric application

Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.

Supplied: bottles of 15, 30, and 60 cc. with graduated dropper.

Also available: VIFORT Capsules, bottles of 30 and 100.

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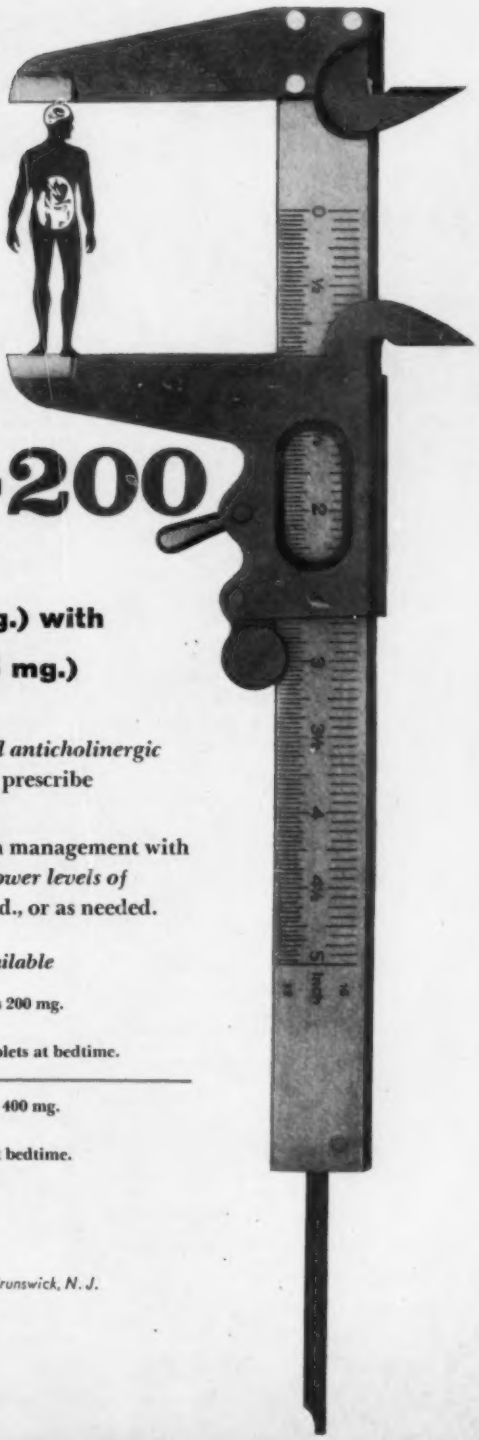
NEW G.I. DOSAGE FORM

FOR DOSAGE ADJUSTABLE TO

THE MEASURE OF THE MAN



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200 mg. Miltown® + 25 mg. anticholinergic

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...When the G. I. patient requires *increased anticholinergic effect* with normal levels of tranquilization, prescribe 2 Milpath 200 t.i.d., or as needed.

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Two dosage forms of Milpath are now available

MILPATH 200—Each yellow, coated tablet contains 200 mg. meprobamate and 25 mg. tridihexethyl chloride.

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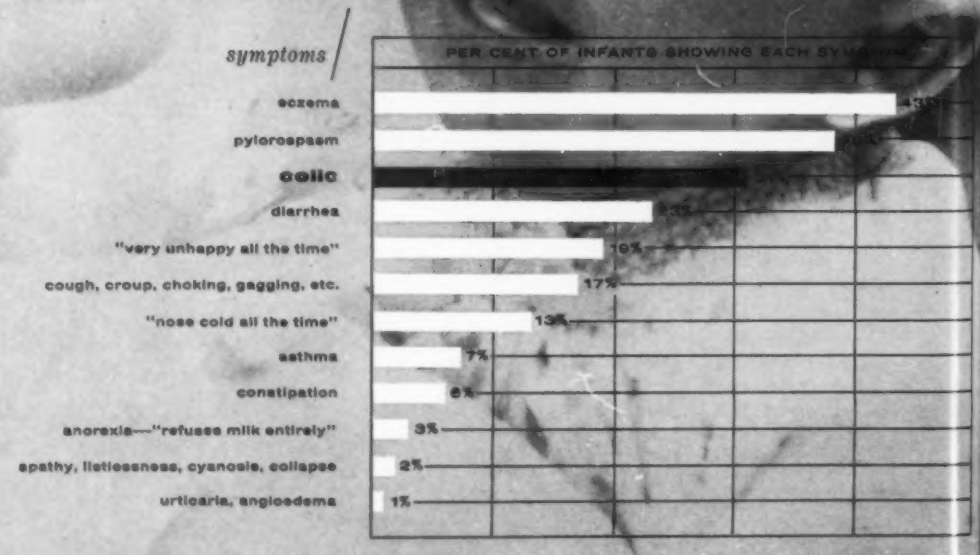
WALLACE LABORATORIES *New Brunswick, N. J.*

minimize the problems of cow's milk allergy

Varied symptoms of cow's milk allergy observed in 206 infants[1]



All symptoms relieved by substituting soya formula for cow's milk formulas

specify **Sobee**

relieve "Colic" *and other symptoms in the milk-allergic infant...*

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Satisfactory results were achieved[2] in the management of gastrointestinal allergic symptoms in infants and children by use of a soya preparation.

All of the infants suffering from "colic" in a clinical study[1] were promptly relieved of their symptoms after being placed on soya formula.

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When allergic tendencies exist in the parents or siblings, it is advisable to start the "potentially allergic"[3] newborn on a milk substitute, such as Sobee.

for diagnosis

When cow's milk allergy was suspected from the presenting symptoms, it was found that "it was simpler and easier to remove cow's milk from the diet for a twenty-four to forty-eight hour trial period and substitute soybean milk than start an allergic study . . ."[1]

1. Clein, N. W.: Pediat. Clin. North America, Nov., 1954, pp. 949-962.
2. Casparis, H.: Ann. Int. Med. 7: 625 (Nov.) 1933.
3. Glaser, J.: Allergy in Childhood, Springfield, Ill., Charles C Thomas, 1956, chap. 67, p. 494.

to relieve milk-allergy symptoms while maintaining sound nutrition

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Hypoallergenic soya formula, Mead Johnson

liquid • "instant" powder

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Symbol of service in medicine

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forestall the epileptic personality

Fear of seizures, parental attitudes and social rejection all threaten the epileptic child. Brain damage or the abnormal discharge itself may provoke psychic disorders.

Better control of seizures and better understanding by parents before a child starts school may prevent the development of an epileptic personality.

Highly effective: In most types of seizures, especially major motor seizures, **MEBARAL** is one of the safest and best anticonvulsants for children.[1] This antiepileptic does not tend to lower learning capacity as may phenobarbital or bromides.[2]

Greater safety: Of the barbiturates, "Mebaral is much less likely to cause hyperactivity in young children."[3] Toxic reactions or ill effects from it are rare.[3,4] In fact, "Mebaral is the least toxic of all the standard anticonvulsant medications. . . ."[5]

MEBROIN,* combining Mebaral and diphenylhydantoin, is truly synergistic[6]— and side effects are only *one half* as frequent as in phenobarbital-diphenylhydantoin mixtures.[7,8] Each relatively tasteless Mebroin tablet contains 90 mg. Mebaral and 60 mg. diphenylhydantoin. Mebroin brings maximal control of seizures with minimal toxicity.[7-10]

Mebaral dosage: CHILDREN under 5 years, from ¼ to ½ grain three or four times daily; over 5 years, from ½ to 1 grain three or four times daily. ADULTS, from 6 to 9 grains daily.

Mebroin dosage: CHILDREN under 6 years, ½ tablet once or twice daily; over 6 years, 1 tablet two or three times daily. ADULTS, 1 or 2 tablets three times daily (average dosage).

For epilepsy at any age

MEBARAL®

Supplied: **MEBARAL** tasteless tablets of 200 mg. (3 grains), 100 mg. (1½ grains), 50 mg. (¾ grain), 32 mg. (½ grain). Bottles of 100.

MEBROIN virtually tasteless tablets. Bottles of 100.

Bibliography: **1.** Livingston, Samuel: The Diagnosis and Treatment of Convulsive Disorders in Children, Springfield, Charles C Thomas, 1954, p. 189. **2.** McCullagh, W. H.: *J. Florida M. A.* 41:718, March, 1955. **3.** Chao, D. H.-C.: *M. Clin. North America* 42:461, March, 1958. **4.** Perlstein, M. A.: *Pediat. Clin. North America* 3:1079, Nov., 1957. **5.** Berris, H.: *Neurology* 4:116, Feb., 1954. **6.** Weaver, L. C.; Swinyard, E. A., and Goodman, L. S.: *J. Pharmacol. & Exper. Therap.* 110:52, Jan., 1954. **7.** Meller, R. L., and Resch, J. A.: *Postgrad. Med.* 6:452, Dec., 1949. **8.** Meller, R. L., and Resch, J. A.: *Bull. Univ. Minnesota Hosp.* 20:78, Oct. 8, 1948. **9.** Chao, D., and Druckman, R.: Convulsive Disorders in Children, In Conn, H. F., ed., Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957, p. 505. **10.** Reder, E. L.: *New York J. Med.* 54:1659, June 1, 1954.

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Mebaral (brand of mephobarbital) and Mebroin, trademarks reg. U. S. Pat. Off.

Why Claysorb means more effective antidiarrheal treatment

In both POLYMAGMA and POLYMAGMA Plain, the new agent Claysorb* gives you a previously unattainable adsorptive power . . . proved to be five times beyond that of kaolin in removing diarrhea-causing toxins.[1] In addition, POLYMAGMA and POLYMAGMA Plain protect the irritated intestinal walls, promote well-formed stools, help restore healthy intestinal function.

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For bacterial diarrhea—
bactericidal against many pathogens

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same formula but without antibiotics

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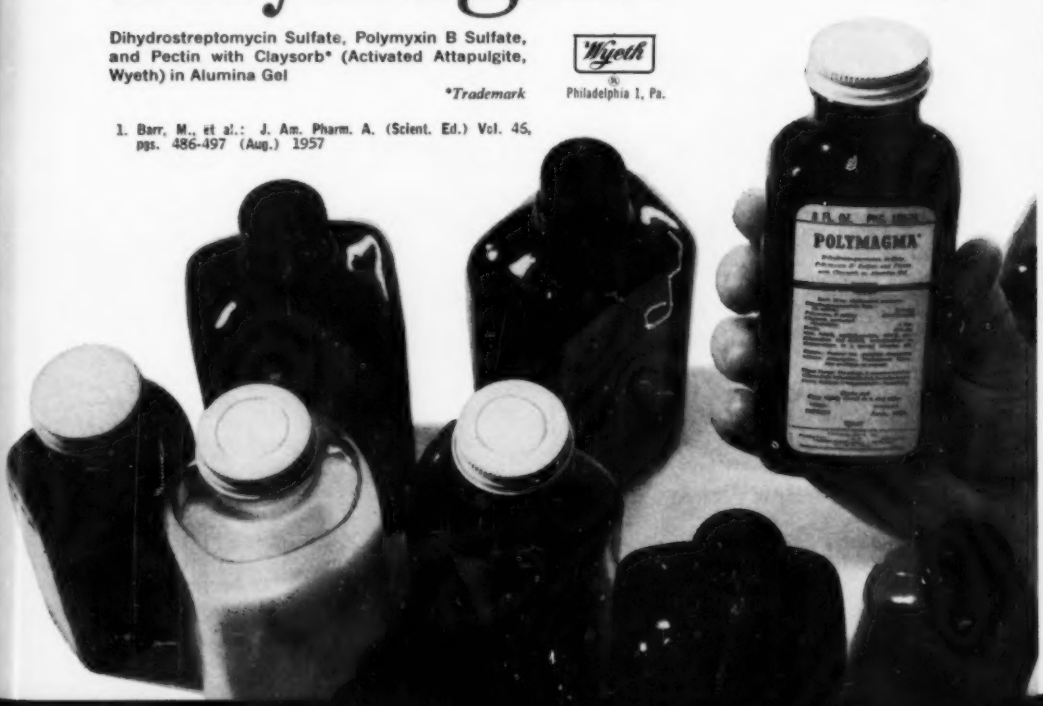
1. Barr, M., et al.: J. Am. Pharm. A. (Scient. Ed.) Vol. 45, pgs. 486-497 (Aug.) 1957



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for *instant* mashed banana in daily routine feeding!

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The addition of three parts water or milk will INSTANTLY provide the wholly-nutritious mashed banana you prescribe.

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new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions

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Cleared in 5 days

Mycolog ointment

Kenalog, Spectrocin and Mycostatin in Plastibase

antipruritic/anti-inflammatory/antibacterial/antifungal

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Cleared in 20 days

Mycolog Ointment – containing the new superior topical corticoid Kenalog – reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

> **"Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[5]**

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation[1-4] – neomycin and gramicidin for powerful antibacterial action[7] – and nystatin for treating or preventing Candida (Monilia) albicans infections.[8,9]

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, H.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H., Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy 3:153 (Nov.) 1958. • 6. Smith J.G., Jr., Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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Despite great general and specific advances that have been made in dermatologic therapy in recent years, the larger part of effective treatment of cutaneous diseases is still based on long-established principles and well-known agents of topical therapy. This is especially true in pediatric dermatology where oral and injectable drugs and physical therapeutic modalities have special difficulties and hazards which limit their usability. More emphasis therefore has been placed and more detail given on the art and science of nursing and medicating the skin than will be found in most books. Systematic medication and nonmedicinal agencies have not been neglected; they are cited briefly in proper dosage, for proper indication, and with proper techniques and safeguards. Topical treatment, however, requires in addition to prescription of agents, methods of use that have to be learned, have to be described, and have to be taught repeatedly to patients. Good practice of topical therapy is a matter both of knowledge and of ingenuity in imparting some of that knowledge in an understandable way to lay persons.

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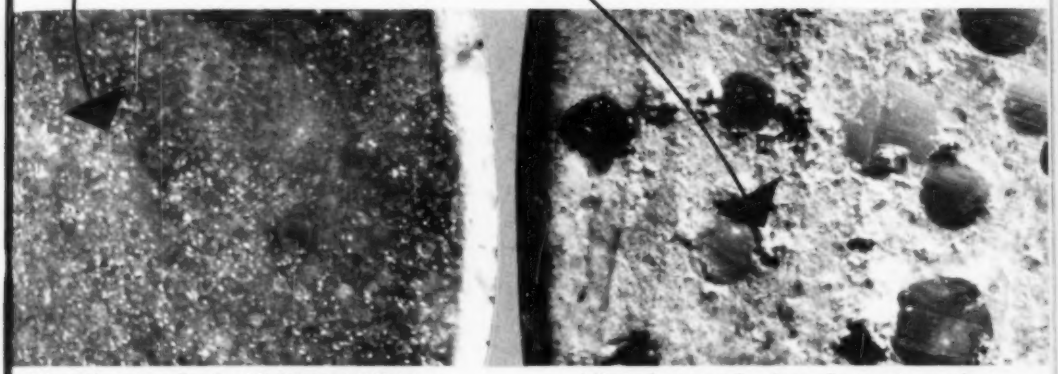

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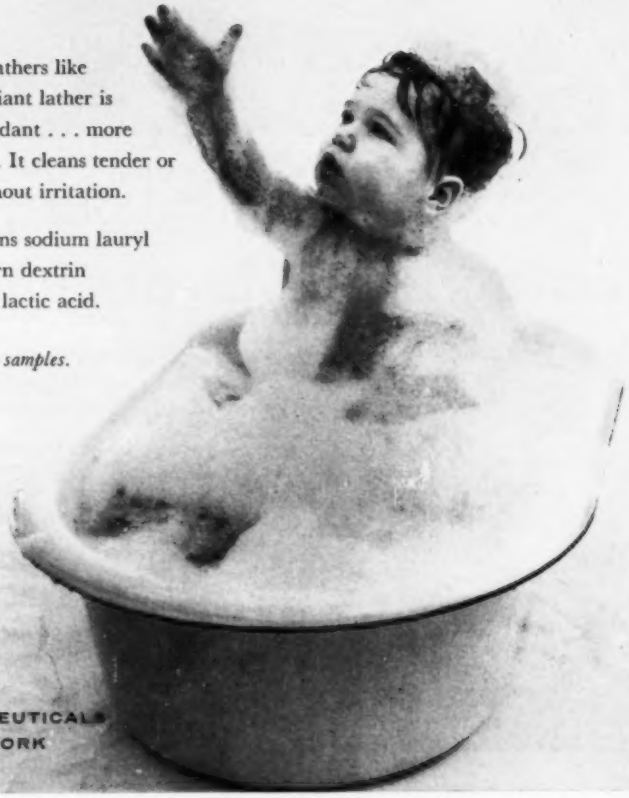

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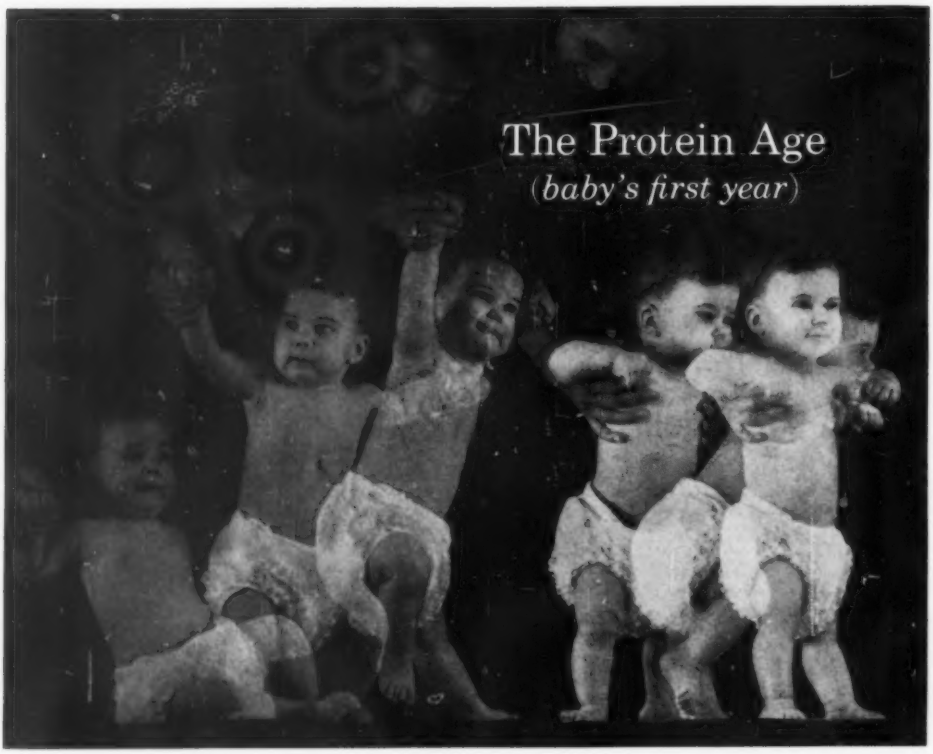

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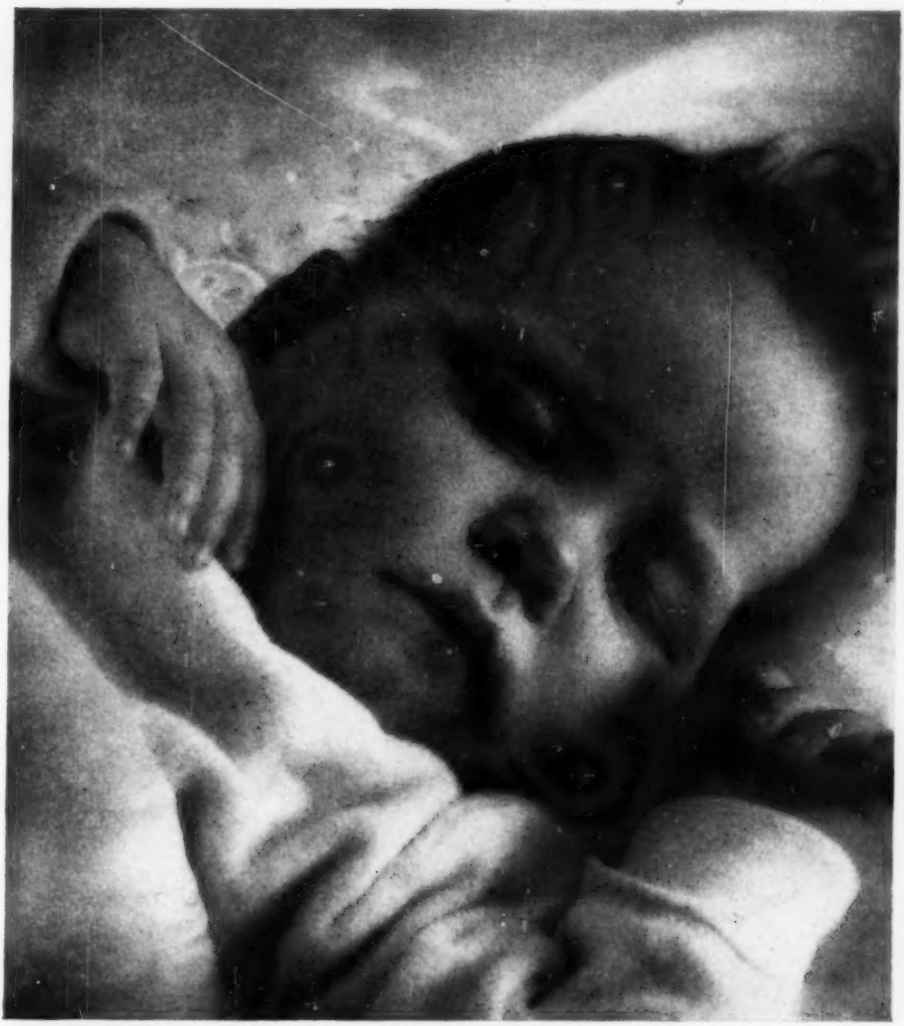

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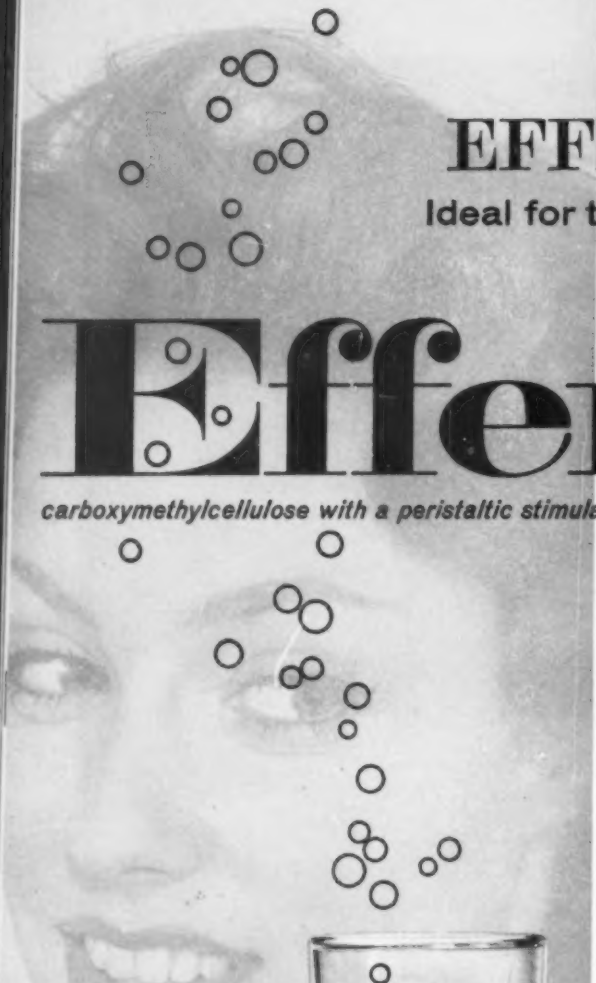

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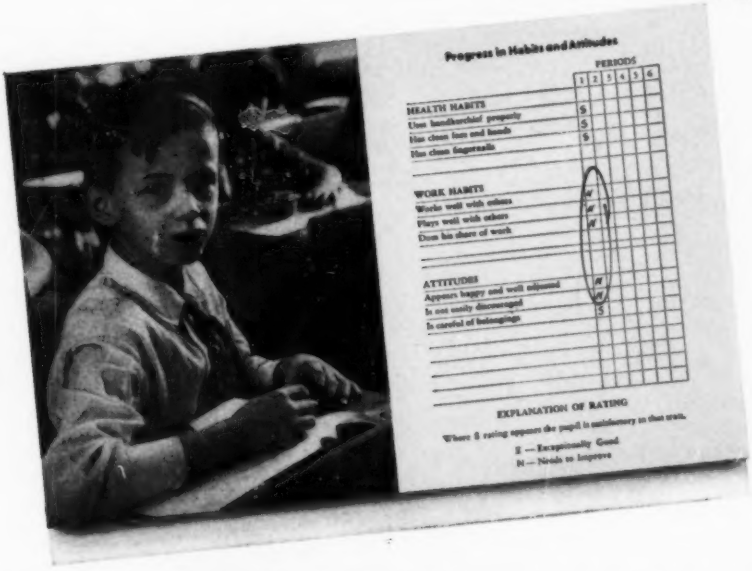
Progress in Habits and Attitudes
PERIODS
1 2 3 4 5 6
HEALTH HABITS
Uses handkerchief properly
Has clean hair and hands
Has clean fingernails
WORK HABITS
Works well with others
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References: 1. Nathan, L. A., and Andelman, B. M.: Illinois M. J. *112*:171 (Oct.) 1957. 2. Bayart, J.: Presented at International Congress of Pediatrics, Copenhagen, Denmark, July 22-27, 1956. 3. Ayd, F. J., Jr.: California Med. *87*:75 (Aug.) 1957.

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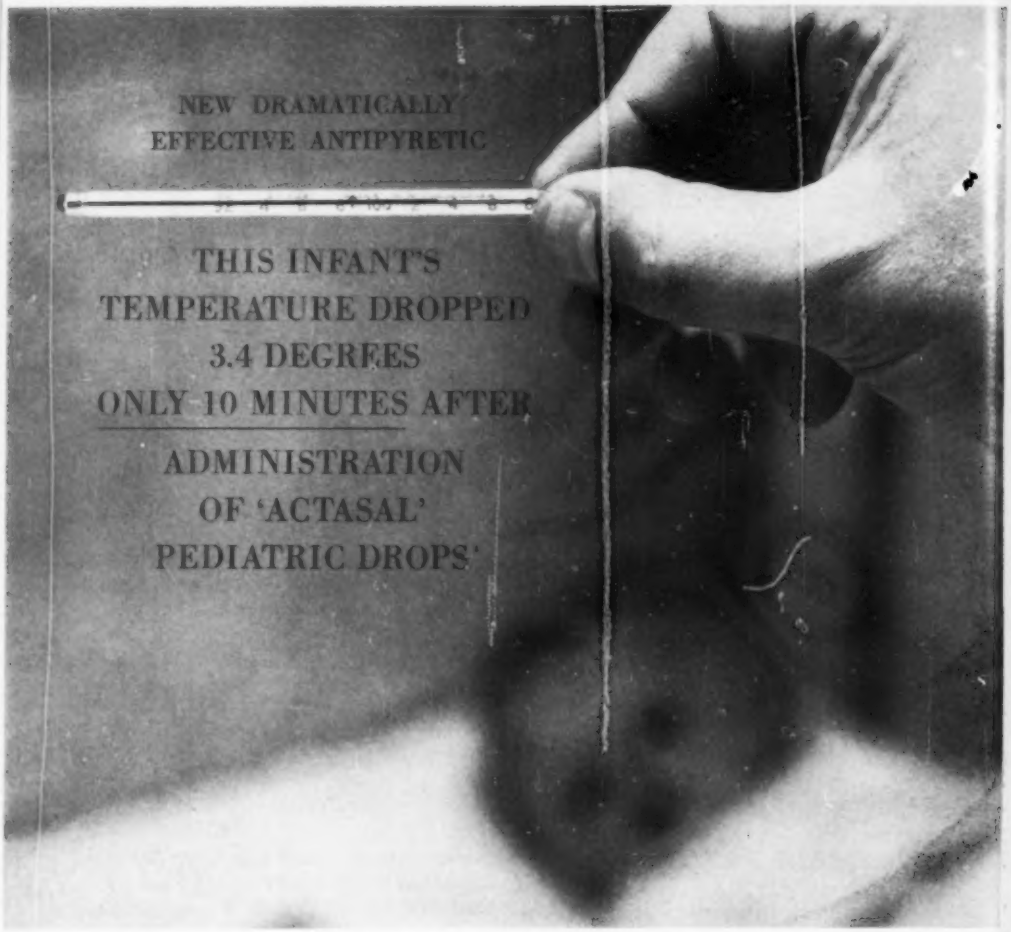

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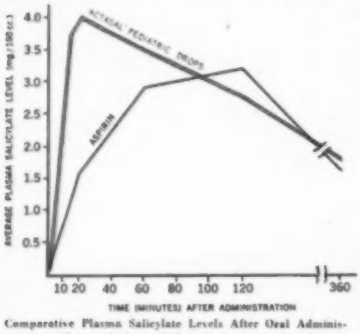

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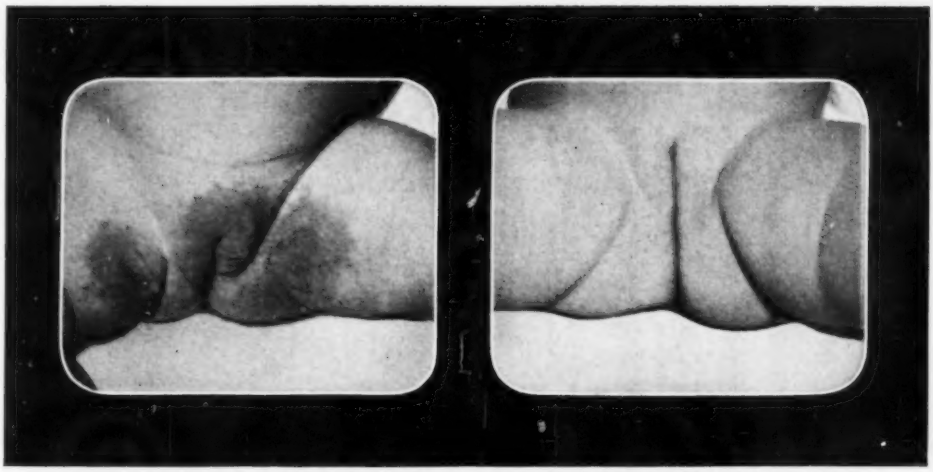

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1. Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954.
2. McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955.
3. Frykman, Howard M.: Minnesota Medicine, Vol. 38, No. 1, January 1955.

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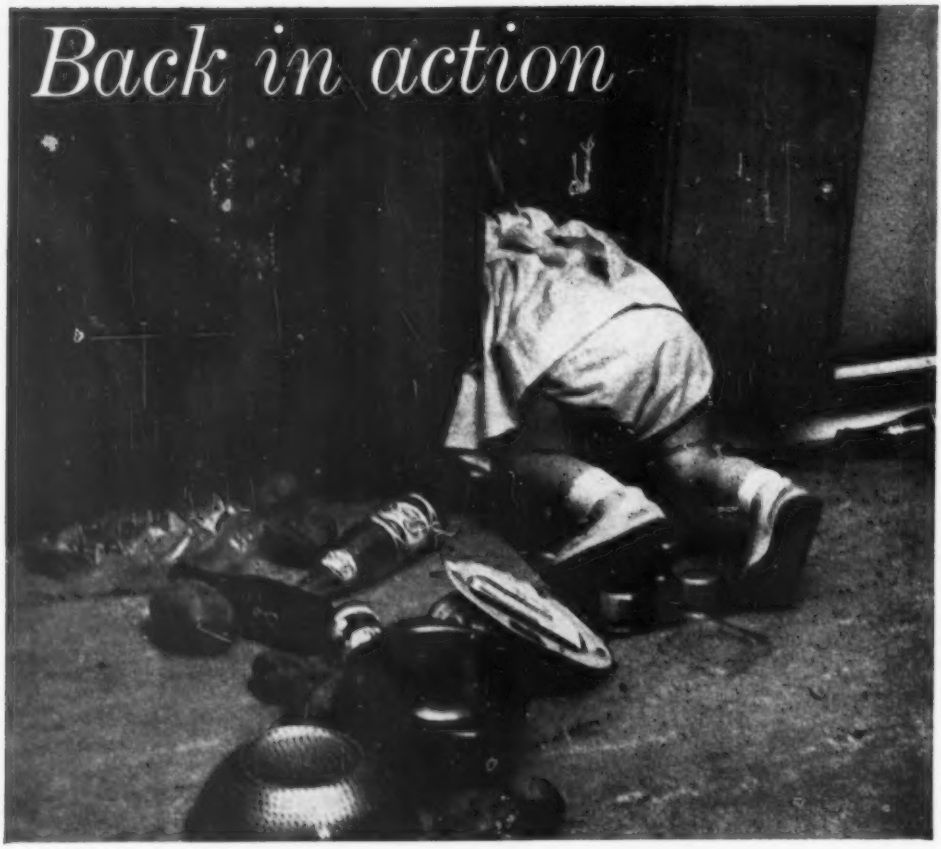

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References: 1. L. S. Goodman and A. Gilman, The Pharmacological Basis of Therapeutics, New York, The Macmillan Co., ed. 2, 1956, p. 1316. 2. C. Rieser in Conn, H. F., Ed., Current Therapy 1959, Philadelphia, W. B. Saunders Co., 1959, p. 361. 3. O. S. Lowsley and T. J. Kirwin, Clinical Urology, ed. 3, Baltimore, The Williams & Wilkins Co., 1956, vol. 2, p. 975. 4. E. J. Richardson in Conn, H. F., Ed., Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957, p. 330.

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FROM MARKED IMPROVEMENT
to COMPLETE CONTROL
of GRAND MAL SEIZURES
with

"MYSOLINE"®

BRAND OF PRIMIDONE

wide margin of safety

CLINICAL EVALUATION OF 486 EPILEPTIC PATIENTS* SHOWED THAT:

In patients who had received no previous anticonvulsant medication,
"Mysoline" therapy alone provided marked improvement to complete control of major motor attacks in the majority of patients.

In patients only partially controlled with maximum dosages of other anticonvulsants,
the addition of "Mysoline" therapy was followed by marked improvement to complete control of grand mal attacks in 39% of the patients.

In patients refractory to maximum dosages of other anticonvulsants,
"Mysoline" employed alone provided marked improvement to complete control of major motor attacks in 54% of the patients.

In 39 patients with mixed seizures,
"Mysoline" provided improvement to marked control in 49% of the patients.

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Literature on request.

*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

5933

Ayerst

AYERST LABORATORIES

New York 16, N. Y. Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd

Every dermatological blemish can be concealed w/ Covermark.

◆

Sympathy alone will not help this child, and the many others who have disfiguring nevi, vitiligo, birthmarks and other dermatological abnormalities. But an application of Covermark *will* change their appearance.

You, Doctor, can help these children and the many persons with unsightly skin discolorations. Recommend the only satisfactory product which completely conceals every type of dermatological malformation.

Waterproof Covermark is a neutral cream, opaque, waterproof and sunproof, and will not crack or flake. It is supplied in eight shades – to match the normal skin tones of your patient.

Covermark should be used to conceal dermatological abnormalities such as in psoriasis, vitiligo, post-operative scars, varicose veins, angioma simplex, and all other types of skin discolorations.

How Supplied

Easy to apply, Waterproof Covermark is supplied in eight shades and in 1 oz., and 3¼ oz. jars. Covermark, in Waterproof form, may be used when the patient goes swimming, or if subject to much perspiration.

Note: Minor skin blemishes are easily concealed with Spotstik – which is Covermark in stick form.

Professional Data supplied to physicians upon request. Available through your pharmacist upon your recommendation, and at leading department stores. For more detailed information write direct to:

Case History

K. M., Age 3 mths. M.*

Examination of infant revealed nevus of extreme proportions on face and neck. Removal was not recommended. Waterproof Covermark was prescribed. Weekly examinations of child showed that Waterproof Covermark completely covered the blemish in such a manner as to give the appearance of an unmarked infant. There were no allergic manifestations or skin irritations that could be attributed to the daily use of Covermark.

◆ **These are unretouched photographs of an actual case, infant K. M., age 3 mths. Covermark applied, K. M., age 6 mths.**

***Reference:** Mayer, D. McC., and Swanker, W. A.: Anomalies of Infants and Children. New York, McGraw-Hill Book Co., Inc., p. 97. 1958

Lydia O'Leary INC.
Dept. P., 41 E.57th St., New York 22, N.Y.

Do Not Confuse it with Tranquilizers

Deaner®

p-acetamidobenzoic acid salt of 2-dimethylaminoethanol

Deaner **is a gentle, slow-acting antidepressant—a totally new molecule. It counteracts mild depression, thereby differing from tranquilizers or sedatives which may aggravate depression.**

Deaner **is unlike ordinary stimulant drugs in that it gradually leads to increased useful energy and alertness, clearer mentation and emotional normalization.**

Deaner **does not produce the undesirable side effects of amphetamine-like drugs...no hyperirritability or jitteriness, no excessive motor activity, no loss of appetite, no elevation of blood pressure or heart rate, no letdown on discontinuance.**

Deaner **is indicated in a wide variety of disturbances associated with or caused by mild depression. It is compatible with virtually all other medications.**

Deaner **also finds a broad area of usefulness in children with short attention span, behavior problems, and learning defects.**

Contraindications: Grand mal epilepsy or mixed types of epilepsy with a grand mal component.

DOSAGE: Initially, 1 tablet (25 mg.) daily in the morning. Maintenance dose, 1 to 3 tablets; for children, ½ to 3 tablets. Full benefits may require two weeks or more of therapy.

'Deaner' is supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol as the *p*-acetamidobenzoic acid salt. In bottles of 100.

In Mild Depression

and many other emotional and behavioral problems

Riker NORTHRIDGE, CALIFORNIA

A SPOON LICKIN' GOOD SULFA!

it's delicious cherry-flavored for children

KYNEX®

ACETYL PEDIATRIC SUSPENSION

N¹ Acetyl Sulfamethoxypyridazine Lederle

just 1 dose a day... achieves rapid therapeutic levels... sustained for 24 hours... extremely low incidence of sensitivity reactions and renal complications... convenient, highly economical...

ALWAYS ACCEPTABLE... WHENEVER SULFAS ARE INDICATED

Recommended dosage: first-day dose is 1 teaspoonful (250 mg.) for each 20 lbs. body weight up to 80 lbs. For each day thereafter, ½ teaspoonful for each 20 lbs. For 80 lbs. and over, use adult dosage of 4 teaspoonfuls (1.0 Gm.) initially, and 2 teaspoonfuls (0.5 Gm.) daily thereafter. Administer immediately after a meal.

Supplied: Each teaspoonful (5 cc.) contains 250 mg. of sulfamethoxypyridazine activity. Bottles of 4 and 16 fl. oz.

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

ONLY

DESITIN®

Medicinal and Nursery

POWDER

is saturated with high grade Norwegian Cod Liver Oil (plus its vitamins A and D)... so will not "dry out" the skin, nor deprive it of its natural fats.

Instead... DESITIN POWDER acts to keep baby's skin normally lubricated, soft, smooth, **supple**..... in **diaper rash**

prickly heat rash
chafing, skin irritations

Every baby deserves the tender, loving care of soothing, protective, **healing** DESITIN POWDER.

Mothers will appreciate your recommendation of both DESITIN POWDER and DESITIN OINTMENT.

samples cheerfully sent—write **DESITIN CHEMICAL COMPANY**
812 Branch Ave., Providence 4, R. I.

DESITIN SOAP ... ideal for baby's bath!

prevention • treatment

Caldesene®
medicated powder

The medication makes the big difference: Caldesene contains 15% calcium undecylenate for sustained antibacterial and antifungal action – Caldesene forms a protective coating which prevents moisture or other irritants from coming into contact with tender or affected areas. Since the film is discontinuous it does not interfere with insensible perspiration. This unique product relieves itching, soreness and burning, and protects against diaper rash, prickly heat, and chafing.

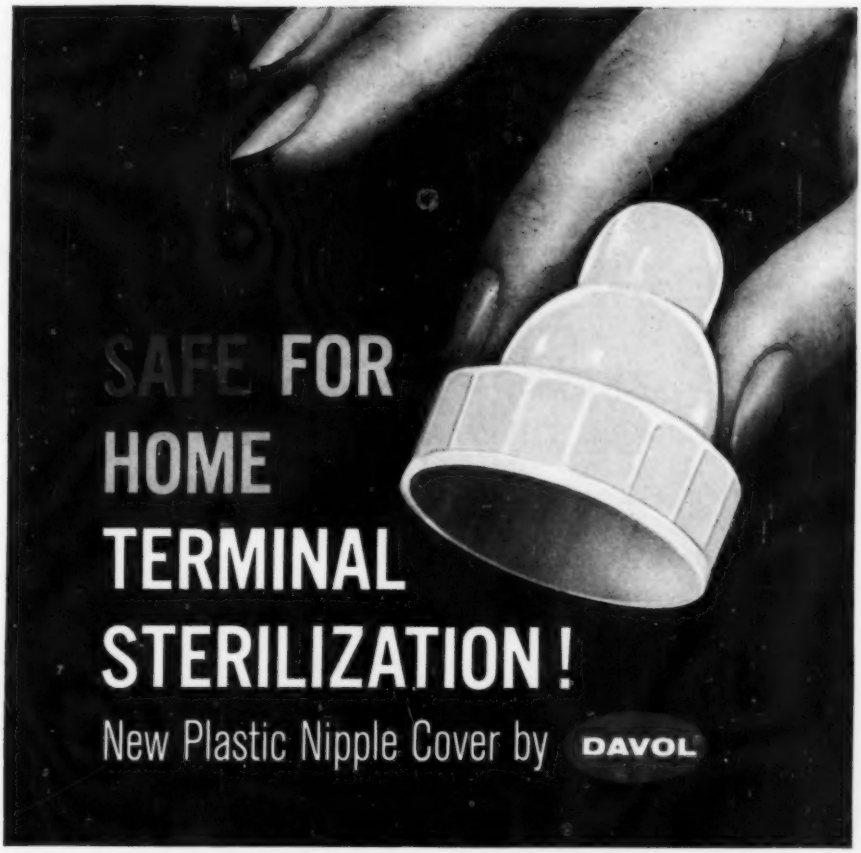
Supplied in 2 oz. shaker containers.

FOR A TRIAL SUPPLY WRITE TO
PROFESSIONAL SERVICE DEPARTMENT

Maltbie

MALTBIE LABORATORIES DIVISION
WALLACE & TIERNAN, INC.

Belleville 9, New Jersey



Davol Nipple Covers, made of sturdy Marlex, are laboratory tested to withstand the pressure of Terminal Sterilization up to 250°F. They enable mothers to use the safe, convenient hospital method of sterilizing with nipples upright – and they keep nipples and formula *sterile* up to feeding time. Fingers need *never touch* the nipple.

The Davol Feed-Rite Nurser is made completely of Marlex plastic – laboratory tested not to break, leak or warp. Marlex resists bacteria . . . will not absorb odors or tastes. Pure white plastic, it's easy to clean – inside and out. Wonderfully light weight for holding and traveling.

Davol Feed-Rite Plastic and Duraglas Nursers feature the exclusive Davol Nipple Cover.

DAVOL BABY PRODUCTS
Designed
with Baby in Mind

DAVOL RUBBER COMPANY
PROVIDENCE 2, R. I.

Announcing

PROZINE*

meprobamate and promazine hydrochloride, Wyeth

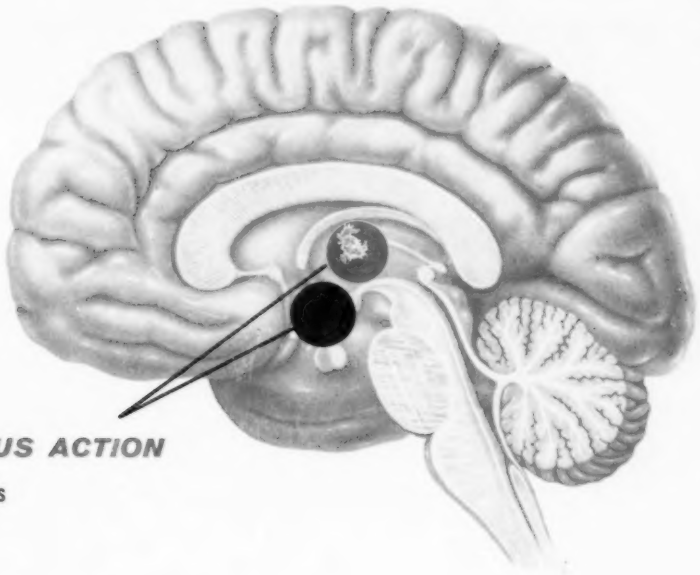
SPECIFIC CONTROL OF EMOTIONAL DISTURBANCES THROUGH DUAL ACTION

PROZINE controls anxiety and tension as well as motor excitability. This effect on the components of emotional reaction is possible because of the dual sites of action of PROZINE—the thalamic and hypothalamic areas of the brain. The unique dual action of PROZINE enables the physician to exert more specific control over emotionally disturbed patients.

PROZINE controls emotional disturbances manifested by apprehension and agitation, insomnia, nausea and vomiting, gastrointestinal symptoms, alcoholism, menopausal symptoms, premenstrual tension.

PROZINE is indicated in patients having a primary emotional disturbance, in patients having an emotional disturbance unrelated to their organic disease, and in patients emotionally disturbed by primary organic disease. PROZINE is especially useful in overly apprehensive medical patients—including surgical and obstetrical—and in emotional problems of children, adolescents, and the aged. It also is useful in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, and hormones (estrogens and corticoids).

*Trademark



SIMULTANEOUS ACTION

of two psychotropic drugs
affecting two areas
of the brain, produces
more **SPECIFIC CONTROL**

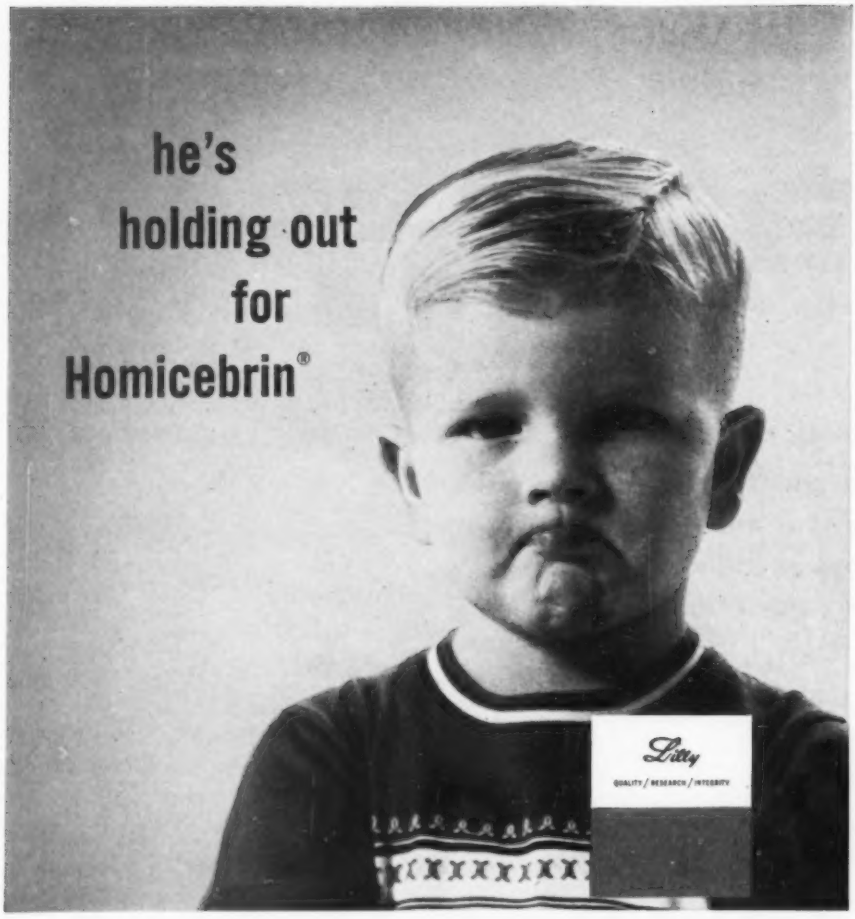
PROZINE in the recommended dosage (1 or 2 capsules, 3 or 4 times daily) produces more specific control than is obtainable with high doses of other ataractic agents.

thus ***in emotionally disturbed patients*** on **PROZINE** the dose required is diminished to the point where the incidence of side-effects and toxicity reactions is minimal* and the patient is calm, tranquil, and amenable to additional therapy, whether it be educational, medical, or psychiatric.

Supplied: Bottles of 50 capsules, each containing 200 mg. of meprobamate and 25 mg. of promazine hydrochloride.
Comprehensive literature available

Wyeth
Philadelphia 1, Pa.

*In studies involving 972 patients suffering a variety of emotional diseases, related and unrelated to physical ailments, 78 per cent were improved; the incidence of side-effects was only 3.7 per cent.



HOMICEBRIN — homogenized multiple vitamins, taste-tested for "tot-appeal"

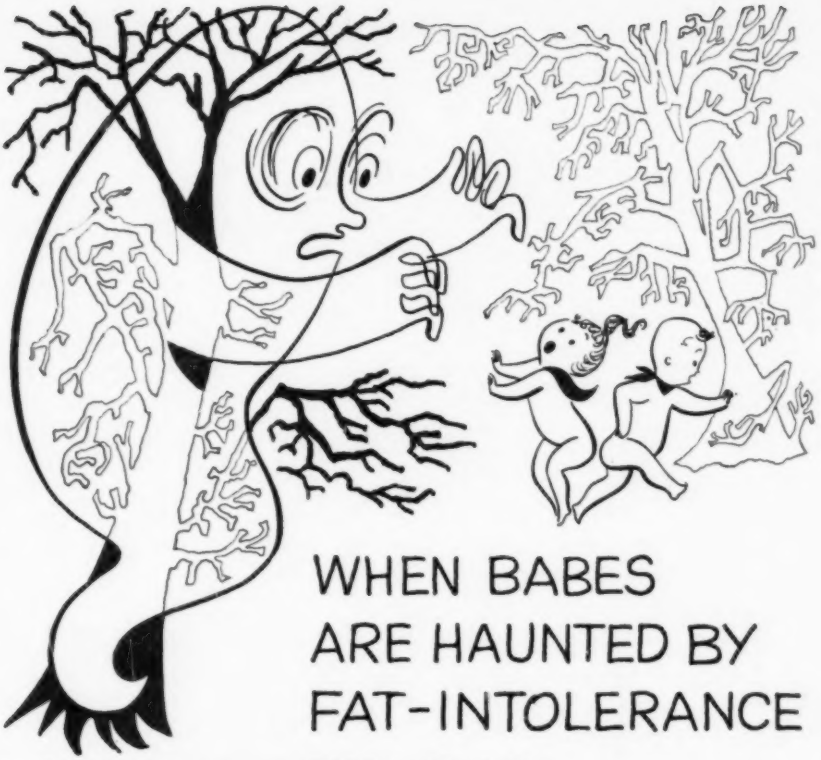
"My vitamins" is the tag young Homicebrin users assign to their personal vitamin supplement. Even the most fastidious of them welcome pleasant-tasting Homicebrin into their daily routine.

This boon to harried parents is also reassuring to the physician. Homicebrin supplies eight essential vitamins, potency-protected by homogenization and careful buffering. To be certain your "tot-age" patients take and receive their full vitamin requirement, specify Homicebrin.

Homicebrin® (homogenized multiple vitamins, Lilly)

LILLY VITAMINS . . . "THE PHYSICIAN'S LINE"

903003



WHEN BABES ARE HAUNTED BY FAT-INTOLERANCE

. . . the physician can count on PET *Instant* Nonfat Dry Milk to banish *one* of the ghosts that beset their path: the problem of adequate milk nourishment.

As a beverage, PET *Instant* is virtually fat-free, yet it supplies the essential milk nutrients—protein, minerals, B-vitamin. With cereals and in cooking, it adds no significant fat of its own and greatly widens the range of foods the child can enjoy.

Happily, PET *Instant* is convenient for the mother to use. It dissolves almost at the touch of water. And costs as little as 8¢ a quart.

Instantized so it dissolves almost at the touch of water.

36.6% Protein (in dry form)
All the calcium and
B-vitamins of whole milk
without the fat

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—PET MILK COMPANY • ST. LOUIS 1, MISSOURI—

NEW

WIDE-SPECTRUM

TOPICAL MICROBICIDE

not an antibiotic . . . not a sulfonamide . . . not a nitrofuran

Triburon

&

Triburon-HC

(containing hydrocortisone 0.5%)

EFFECTIVE EVEN AGAINST ANTIBIOTIC-RESISTANT STRAINS

HIGHLY ACTIVE

■ against "pathogenic cocci [both staphylococci and streptococci] regardless of their resistance to antibiotics."[1]

■ against pathogens common in skin and wound infections.

VIRTUALLY NONSENSITIZING

■ in more than 4500 stringent, closed-patch sensitivity tests, the incidence of allergic response was less than 2 per cent.[2, 3]

■ in initial clinical studies, only 15 of 1014 patients developed evidence of skin irritation.

MINIMAL RESISTANT ORGANISMS

■ laboratory attempts to develop Triburon-resistant strains produced no substantial change in organism sensitivity.[1]

- WIDE-SPECTRUM
- RAPID-ACTING
- NONIRRITATING
- NONSENSITIZING
- NONSTAINING
- ODORLESS

DIAGNOSIS AND NO. OF PATIENTS	DURATION OF TREATMENT	RESULTS	ADVERSE REACTIONS
Impetigo contagiosa (50)	Triburon 3-10 days	excellent	none
Ecthyma (24)	Triburon 5-14 days	excellent	none
Pustular folliculitis (16)	Triburon 1-3 weeks	infection controlled	3 complaints of burning
Dermatitis repens (18)	Triburon 1-2 weeks	infection controlled	none
Dermatitis repens (18)	Triburon-HC 1-4 weeks	excellent	none
Secondarily infected eczematous eruption (20)	Triburon 1-2 weeks	infection controlled	none
Secondarily infected eczematous eruption (64)	Triburon-HC 1-4 weeks	excellent	1 complaint of irritation

Chart based on finding of E. Edelson, E. Grunberg and T.V. Morton Jr.

PACKAGES:
Triburon Ointment, 1-oz tubes and 1-lb jars.
Triburon-HC Ointment, 5-Gm and 20-Gm tubes.

REFERENCES: 1. R. J. Schnitzer, E. Grunberg, W. F. DeLorenzo and R. E. Bagdon, to be published.
2. E. Edelson, E. Grunberg and T. V. Morton, Jr., Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959.
3. R. C. V. Robinson and L. E. Harmon, Antibiotics Annual 1958-1959.

TRIBURON™: triclobisonium chloride — N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyl]-N, -N'-dimethyl-1,6-hexanediamine bis (methochloride). ROCHE®

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10 • New Jersey

EFFICIENT PEDIATRIC PRODUCTS

Quadrupled Sulfonamide Therapy

In the efficient management of infectious diseases of children, four time-tested sulfas confer multiple therapeutic advantages . . . at fractional dosage of each . . . for maximum potency, greater solubility in urine, prolonged high blood concentrations and minimum risk of crystalluria. Delicious coconut-custard flavored suspension, pints and gallons—or tablets, bottles of 100 and 1000.

Each dose contains Sulfadiazine 0.167 Gm Sulfamerazine 0.167, Sulfamethazine 0.056 Gm, Sulfacecetamide 0.111 Gm

Complete literature to physicians on request.

KATRASUL

Highly Effective Anthelmintic

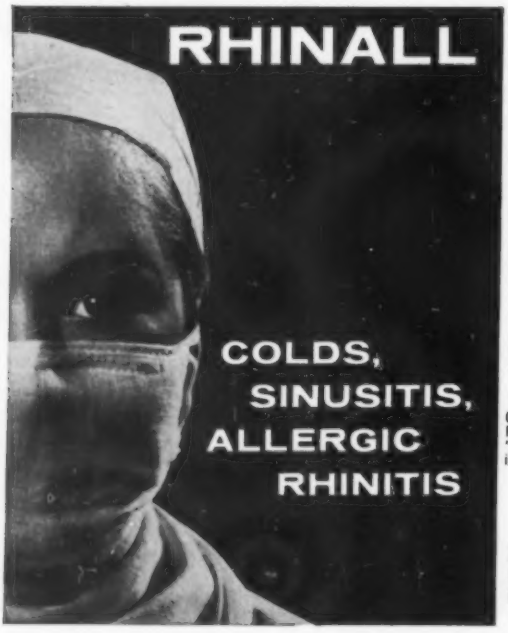
Vermizine's principal ingredient, piperazine gluconate, quickly and effectively halts and eliminates pinworm and roundworm infestation in children and adults.

Pleasantly strawberry-flavored for ready patient acceptance, Vermizine is administered on a basis of body weight, and according to a predetermined daily dosage schedule. Usual hygienic and sanitary measures should be employed with all patients. It is well tolerated, economical, safe and effective. Try it, doctor, in your next troublesome case. Available in pints and gallons.

Piperazine gluconate equiv. to 100 mg piperazine hexahydrate/cc

VERMIZINE

CHICAGO PHARMACAL COMPANY • CHICAGO, ILLINOIS



NOSE DROPS

For quick, effective relief of nasal congestion

Safe for both children and adults, Rhinall Nose Drops are pleasant to use, provide ventilation and drainage without irritation of the ciliated epithelium.

- *no burning or irritation*
- *no risk of sensitization*
- *no bad taste or after reactions*

SUPPLIED: one-ounce dropper bottle; ½-ounce plastic spray bottle.

Contains:
Phenylephrine Hydrochloride 0.15%
"Propadrine" Hydrochloride 0.3%
in an isotonic saline menstruum

RHINOPTO CO.
3905 Cedar Springs
Dallas, Texas

Cotton-soft comfort...

in Diaper Rash, Routine Baby Care with

TUCKS®

Handy disks of soft cotton flannel, saturated with witch hazel (50%) and glycerine (10%), pH 4.6

Recommend TUCKS...

Wherever and whenever a soft, mildly astringent aid to cleansing and healing is needed...

***TUCKS**...cleanses and soothes irritated surfaces when used as a wipe...cools and comforts the distress of chafing...encourages thorough cleaning*

*Recommend that mother keep **TUCKS** by the crib in their handy jars for routine cleansing after diaper change, and in the diaper bag when baby travels.*

jars of 40 and 100.

Please send me sample supply of TUCKS.

_____ M. D.

Address _____

City _____ Zone ____ State _____

fuller PHARMACEUTICAL COMPANY
MINNEAPOLIS 16, MINNESOTA

STANDARD

for nasal decongestion

Tyzine®

brand of tetrahydrozoline hydrochloride

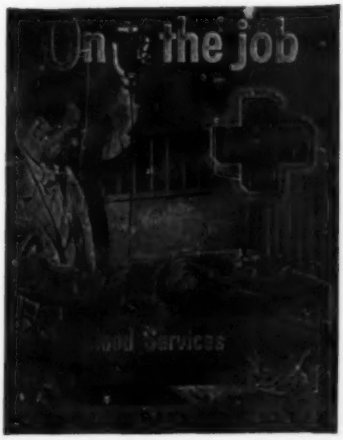
works fast • lasts long • virtually no taste or odor, no sting or burn, no rebound congestion

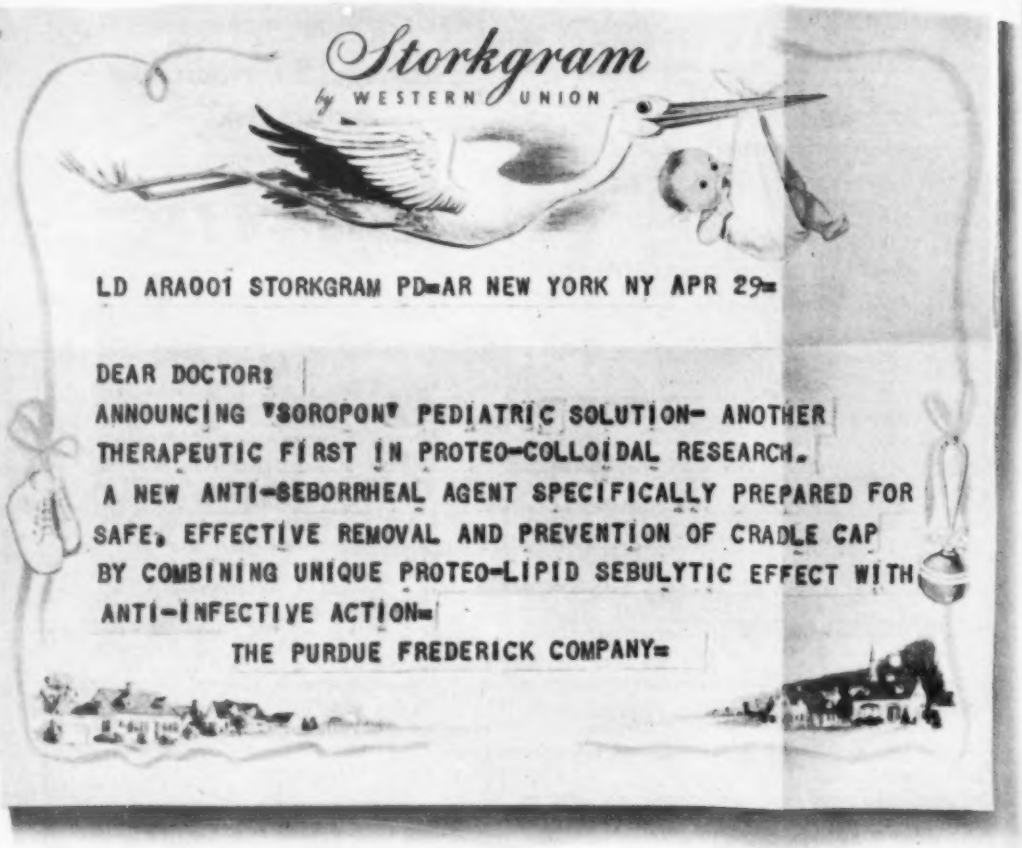
Nasal Solution, 0.1%, 1 oz. dropper bottles.
Nasal Spray, 0.1%, 15 cc., in plastic bottles.
Pediatric Nasal Drops, 0.05%, 1/2 oz. bottles, with calibrated dropper.

Note: Overdosage may cause drowsiness or deep sleep in infants and young children. Use Pediatric Nasal Drops (0.05%) for children under six years. When TYZINE Nasal Spray is administered, it should be held only in an upright position.

Science for the world's well-being

Pfizer PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.




Storkgram
by WESTERN UNION
LD ARA001 STORKGRAM PD=AR NEW YORK NY APR 29=
DEAR DOCTOR:
ANNOUNCING "SOROPON" PEDIATRIC SOLUTION- ANOTHER
THERAPEUTIC FIRST IN PROTEO-COLLOIDAL RESEARCH.
A NEW ANTI-SEBORRHEAL AGENT SPECIFICALLY PREPARED FOR
SAFE, EFFECTIVE REMOVAL AND PREVENTION OF CRADLE CAP
BY COMBINING UNIQUE PROTEO-LIPID SEBULYTIC EFFECT WITH
ANTI-INFECTIVE ACTION=
THE PURDUE FREDERICK COMPANY=

Anti-exudative (CERAPON-C) • attacks the protein component of seborrheal plaques, modifying it so that it will disperse in the propylene vehicle • destroys the "cement" which maintains the seborrheal plaques • emulsifies the lipid component, thereby fragmenting the seborrheal plaques, and permitting easy removal through washing or rinsing.

Antibiotic (TYROTHRICIN) • combats infection associated with seborrhea through unimpeded contact with organisms.

Vehicle (PROPYLENE GLYCOL) • enhances and complements the emulsifying activity of 'Cerapon-C' • allows removal of emulsified and dispersed plaques, through its water miscibility by simple rinsing.

SOROPON T.M.

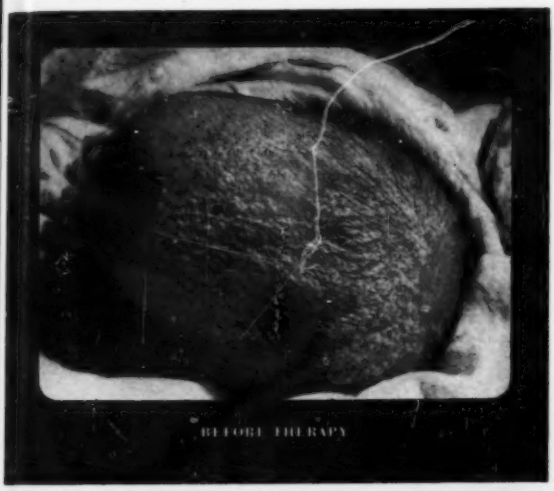
CONTAINS CERAPON-C* 12.0% IN PROPYLENE GLYCOL WITH PARABENS 0.1% AND TYROTHRICIN 0.1%.
*PURDUE FREDERICK BRAND OF TRIETHANOLAMINE POLYPEPTIDE COCOATE-CONDENSATE

PEDIATRIC SOLUTION

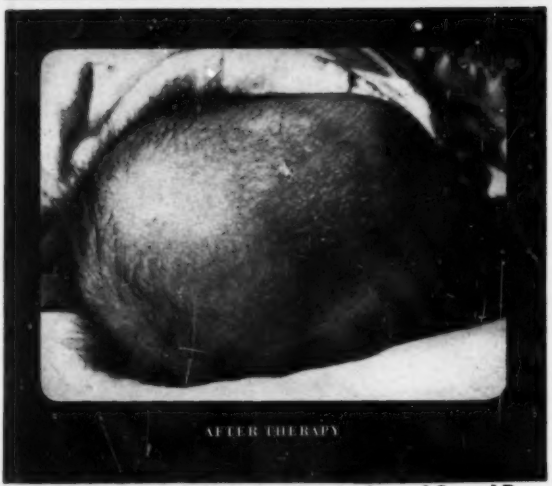
The Purdue Frederick Company

DEDICATED TO PHYSICIAN AND PATIENT SINCE 1892
NEW YORK 14, N.Y. | TORONTO 1, ONTARIO

TYPICAL CASE HISTORY OF CRADLE CAP
CLINICAL RESULTS WITH
'SOROPON' PEDIATRIC SOLUTION



BEFORE THERAPY



AFTER THERAPY

Bialkin, G.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

CASE HISTORY: J. D., a 5 month old white male developed a dry seborrhea capitis at approximately 6 weeks after birth which covered the whole scalp. Concomitantly, there was a severe seborrheic eczema of the face and body. By the time of examination, the child had been treated with various detergent ointment and lotion preparations without apparent effect. 'Soropon' Pediatric Solution was applied as a shampoo, directly to the scalp to remove the encrustations. Repeated applications were necessary for complete removal. Since the scalp was inordinately dry, lanolin creme was prescribed as a topical application after each shampoo. A series of 5 treatments were required for complete removal and after this treatment period the seborrheic eczema of the face and body had virtually disappeared. The patient was symptom free for the past three months. Bialkin, G.: Seborrhea Capitis: Clinical Effectiveness of A New Therapeutic Agent. Arch. of Ped. (to be published).

IMPORTANT: 'Soropon' Pediatric Solution is recommended for use as a routine scalp and hair shampoo to keep the scalp free of excessive oiliness, scaling and dandruff. Spacing of scalp treatments, according to individual needs, will keep the scalp free of accumulated tissue debris, thus minimizing the tendency for more serious scalp and skin conditions to develop.

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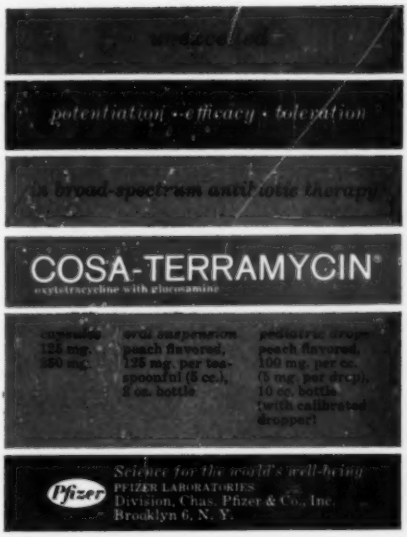

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Thank You!

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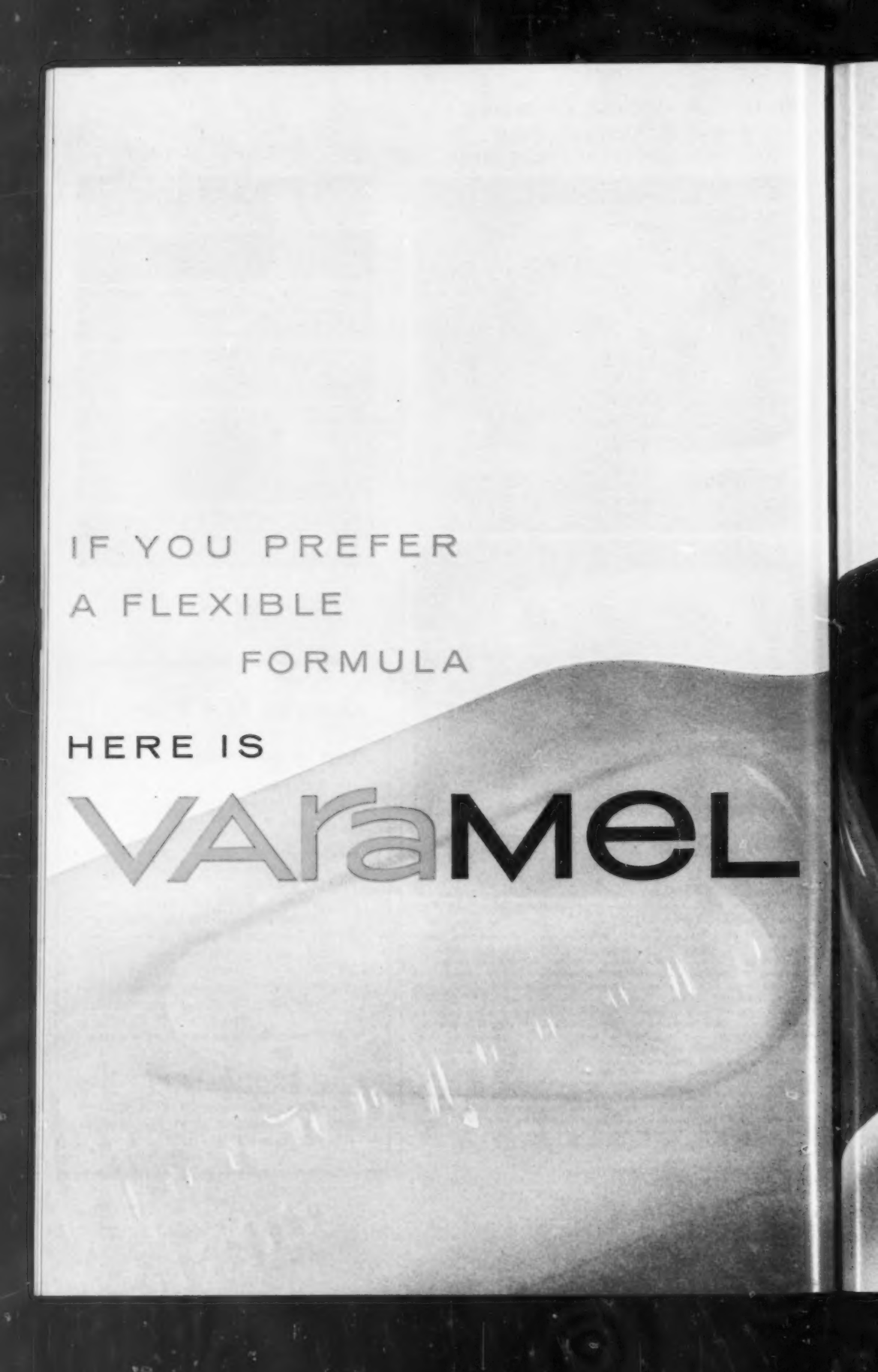
IF YOU PREFER
A FLEXIBLE
FORMULA

HERE IS

VARAMEL



VARAMEL is FLEXIBLE—you adjust water and carbohydrate.

VARAMEL is EASILY DIGESTED—butterfat is replaced.

VARAMEL is ECONOMICAL—contains adequate amounts of all known essential vitamins plus iron.

VARAMEL is ETHICALLY PROMOTED.

THE BAKER LABORATORIES, INC.
Makers of BAKER'S MODIFIED MILK
Cleveland 3, Ohio

VARAMEL

APPROXIMATE ANALYSIS (UNDILUTED)

Protein	4.9%
Carbohydrate (from milk source)	8.3%
Fat	3.8%
Ash	1.2%
Moisture	79.8%

32 Calories per ounce

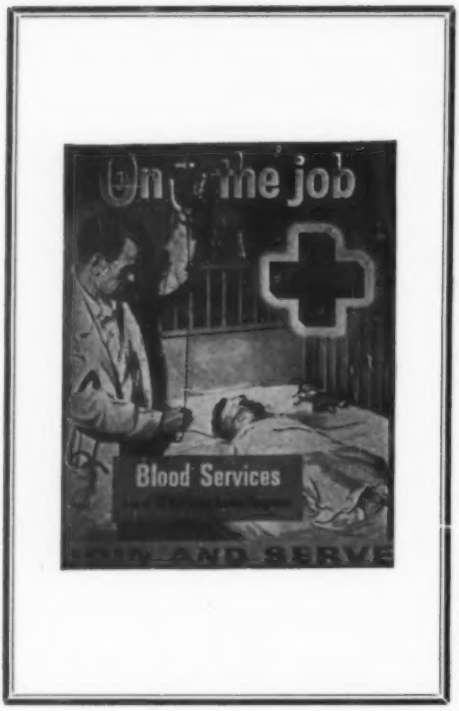
PER QUART AT 1:1 DILUTION

Vitamin A	2500 U.S.P. units
Vitamin D	800 U.S.P. units
Ascorbic acid (C)	50 mg.
Thiamine (B_1)	0.6 mg.
Niacin	10 mg. equiv.
Riboflavin	1.1 mg.
Vitamin B_6	0.16 mg.
Calcium	900 mg.
Iron	7.5 mg.

VARAMEL + WATER + CHO

optimum nutrition

providing all the normal dietary requirements plus a reserve for stress situations.



Viokase Pancreatin 4 times the N.F. X minimum potency standards.

VIOKASE

WHOLE PANCREAS
Not an extract!

EFFECTIVE substitution therapy in demonstrated pancreatic deficiency.

PHYSICIANS' COUNCIL FOR EDUCATION ON CHILD HEALTH
Conforms to Code for Advertising

NOT ENTERIC COATED

Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

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